Impact of gender, sexual orientation and socio-economic factors on HIV treatment outcomes in the UK

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Declaration

I, Lisa Samantha Burch confirm that the work presented in this thesis is my own. Where information has been derived from other sources, I confirm that this has been indicated in the thesis.

Abstract

The effectiveness of antiretroviral therapy (ART) has led to greatly improved prognosis for people living with HIV, such that they now have a similar life expectancy to the general population. However, these improvements over time have not necessarily been seen equally among all demographic groups. The aim of this thesis was to investigate the differences in virological response to ART, treatment adherence, and late HIV diagnosis by gender and sexual orientation among people with HIV in the UK, and assess whether any differences have narrowed in more recent years. Additional analyses explored whether socio-economic factors could explain the observed differences in outcome across gender/sexual orientation groups.

The analyses were based on data from two observational UK studies: the Royal Free HIV Cohort Study and the Antiretrovirals Sexual Transmission Risk and Attitudes (ASTRA) questionnaire study.

Results showed that, among individuals on ART, women and men who have sex with women (MSW) had a higher prevalence of detectable viral load and lower CD4 counts than men who have sex with men (MSM). Similarly, for initial response to first-line ART, virological outcomes were less favourable for women and MSW, compared to MSM even in the most recent years, and there was no evidence that these differences in outcome were narrowing over time. Socio-economic disadvantage (financial hardship; non-employment; renting; unstable housing status; non-university education) was strongly associated with higher prevalence of ART non-adherence and poorer virological outcomes. Socio-economic status explained much of the disparities in treatment outcomes between MSM and women, but less between MSW and MSM. A considerably higher prevalence of late diagnosis was seen among women and MSW compared to MSM.

In conclusion, this thesis identified ongoing disparities in HIV outcomes between gender/sexual orientation groups. Clinical management strategies should focus on demographic and socio-economic groups at risk of poorer treatment outcomes.

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List of abbreviations

3TC	Lamivudine
ABC	Abacavir
ADE	AIDS Defining Event
AIDS	Acquired Immune Deficiency Syndrome
aHR	adjusted Hazard Ratio
aOR	adjusted Odds Ratio
aPR	adjusted Prevalence Ratio
aRR	adjusted Risk Ratio
ART	Antiretroviral Therapy
ARV	Antiretroviral drug
AZT	Zidovudine
BHIVA	British HIV Association
CI	Confidence Interval
d4T	Stavudine
ddC	Zalcitabine
Ddl	Didanosine
DNA	Deoxyribonucleic Acid
DRV	Darunavir
EACS	European AIDS Clinical Society
EEA	European Economic Area
EFV	Efavirenz
FDA	Food and Drug Agency
FTC	Emtricitabine
EU	European Union
HBV	Hepatitis B Virus
HCV	Hepatitis C Virus
HIV	Human Immunodeficiency Virus
HR	Hazard Ratio
ICDC	Ian Charleson Day Centre
IDU	Intravenous Drug Use
InSTI	Integrase Strand Transfer Inhibitor
IQR	Interquartile Range
LPV	Lopinavir
LTFU	Lost To Follow-Up

MSM	Men who have Sex with Men
MSW	Men who have Sex with Women
MTCT	Mother To Child Transmission
NNRTI	Non-Nucleoside Reverse Transcriptase Inhibitor
NRTI	Nucleoside Reverse Transcriptase Inhibitor
NVP	Nevirapine
OI	Opportunistic Infection
OR	Odds Ratio
PI	Protease Inhibitor
PLWH	People Living With HIV
PR	Prevalence Ratio
PWID	People Who Inject Drugs
RCT	Randomized Controlled Trial
RNA	Ribonucleic Acid
RR	Risk Ratio/ Relative Risk
RTV	Ritonavir
SES	Socio-Economic Status
STI	Sexually Transmitted Infection
TB	Tuberculosis
TCVF	Triple Class Virological Failure
TDF	Tenofovir Disoproxil Fumarate
UNAIDS	United Nations programme on HIV/AIDS
VL	HIV-RNA Viral Load
WHO	World Health Organisation

List of relevant study acronyms

ACCESS	AIDS Care Cohort to evaluate Exposure to Survival Services
ANRS	Agence Nationale se Recherches sur le Sida
ART-CC	ART Cohort Collaboration
ASTRA	Antiretrovirals, Sexual Transmission Risk, and Attitudes
ATHENA	AIDS Therapy Evaluation in the Netherlands
CANOC	Canadian Observational Cohort
CASCADE	Concerted Action on SeroConversion to AIDS and Death in Europe
CHASE	Community Health And Safety Evaluation
COHERE	Collaboration of Observational HIV Epidemiological Research Europe
CoRIS	Cohorte de la Red de Investigación en Sida
DHCS	Danish HIV Cohort Study
GEEMA	Grupo Español para el Estudio Multifactorial de la Adherencia
HERO	HIV Epidemiologic Research on Outcomes
HOMER	HAART Observational Medical Evaluation and Research
HOPS	HIV Outpatient Study
IATG	Italian Antiretroviral Treatment Group
ICoNA	Italian Cohort of Naïve Antirerovirals
KPNC	Kaiser Permanente Northern California
LISA	Longitudinal Investigations into Supportive and Ancillary health services
MACH14	Multi-site Adherence Collaboration on HIV
MACS	Multicentre AIDS Cohort Study
MMP	Medical monitoring project
NA-ACCORD	North American AIDS Cohort Collaboration on Research and Design
NHSS	National HIV Surveillance System
NYC HARS	New York City HIV/AIDS Reporting System
OCS	Ontario HIV Treatment Network Cohort Study
RFHCS	Royal Free HIV Cohort Study
SHAS	Supplement to HIV/AIDS Surveillance

SHCS	Swiss HIV Cohort Study
SUN	Study to Understand the Natural History of HIV and AIDS in the era of effective therapy
UK CHIC	UK Collaborative HIV Cohort
VACS	Veterans Aging Cohort Study
WIHS	Women's Interagency HIV study

Chapter 1 Introduction

This chapter provides background information on the natural history of Human Immunodeficiency Virus (HIV), antiretroviral drugs (ARVs) used to treat HIV, the stages in the care continuum, policies and recommendations for HIV screening and treatment in the UK, and details of the current epidemic in the UK. In addition, this chapter introduces the relationship between gender/sexual orientation, socio-economic status (SES), and HIV outcomes.

1.1 Natural history of HIV in the absence of treatment

1.1.1 The life cycle of HIV virions

HIV is a retrovirus: a family of enveloped viruses that replicate in the host cells. More specifically it belongs to the subgroup of lentiviruses or 'slow viruses'[1;2] named because of the long period between infection and the onset of serious symptoms[3]. Once HIV is transmitted, the virus targets and binds to CD4 T-cells. These cells play a vital part in the co-ordination of the human immune system[4]. New viral particles are produced within the cell and are then ready to infect further cells, with a single cell able to produce thousands of infectious HIV particles[3]. Although the exact mechanisms are still not fully understood, through this process, HIV weakens and destroys CD4 T-cells and reduces the ability of the body to replace them[5;6].

1.1.2 The natural history of HIV infection

1.1.2.1 *Transmission*

HIV spreads between individuals via the exchange of bodily fluids including blood, semen, pre-seminal fluid, rectal fluids, vaginal fluids and breast milk. The main transmission routes are: through condom-less sex between men or between men and women[7], and more rarely through oral sex[8]; through intravenous drug use (IDU) using contaminated needles[9]; by mother to child transmission (MTCT) or vertical transmission during pregnancy, birth, or breast feeding[10]; or receiving contaminated blood products[11].

Sexual transmission is the most common route of HIV infection worldwide[12]. The most important factor associated with the risk of sexual transmission of HIV is the sexual partner's HIV-RNA levels – the number of copies of the viral particles (of HIV genetic material) found in each millilitre of plasma. This quantity is also known as the viral load (VL). The higher an individual's VL, the higher the probability of transmission[13;14]. The risk of infection through sexual intercourse is also dependent on: the sexual partner, sexual act, use of preventative methods such as condoms[7], the presence of other

sexually transmitted infections such as the Herpes simplex virus-2 (HSV-2)[15], genetic susceptibility[16], and stage of infection of sexual partner[17]. For transmission via heterosexual sex, the probability of infection per sexual act is as low as one in a thousand for female-male exposure even in the presence of detectable viraemia[18;19], with male-to-female infection twice as likely as female-to-male infection per sexual act[3;20]. In high-income settings, men who have sex with men (MSM) are often the group with the highest reported risk for HIV infection[21]. MSM receptive of anal intercourse are at a higher risk of infection per sexual act with a HIV-positive partner compared with being the insertive partner[7].

1.1.2.2 ***Laboratory markers of HIV***

Two surrogate laboratory markers are primarily used to monitor HIV progression: CD4 cell count and VL (described in Section 1.1.2.1). The normal range for the CD4 count in a healthy individual without HIV is 500-1600 cells/μL[22;23], with values around 100 cells/μL higher for women than for men on average[22].

1.1.2.3 ***Pathogenesis of HIV infection***

In the absence of treatment, the course of HIV infection in an individual can be divided into three main stages: primary (or acute) infection, asymptomatic infection and symptomatic infection/AIDS[24;25]. During primary infection, which lasts for approximately 12 weeks after infection, 70-90% of individuals will experience a seroconversion illness[26;27]. However, the symptoms commonly experienced, such as fever, malaise, night sweats and lymphadenopathy, are frequently confused with general 'flu-like' symptoms[28]. These symptoms generally last days to a week[27]. During this phase, the VL can reach levels up to 10 million copies/μL before declining to a more stable level of around 10000-100000 copies/mL, which is sometimes termed the viral "set point"[29]. High levels of viraemia and mucosal shedding mean that the risk of onwards transmission is at its highest during this time[17;30]. Meanwhile, the CD4 cell count rapidly declines before recovering slightly to a level below that seen prior to infection[6].

Following primary infection is a period of clinical latency. Although it is highly variable from individual to individual, it typically lasts around 10 years[31;32]. During this phase, there is steady but small increase over time in the VL, with a rate of increase between 0.08 and 0.11 log copies/mL per year[33-35]. The CD4 count continues to steadily decline, on average between 1.2 and 1.7 cells/μL per year on the square root scale[33;36], but this is highly variable between individuals. In this latent phase, a person living with HIV is generally asymptomatic and so individuals are likely to remain unaware of their HIV status unless they are tested.

The end of this clinically latent stage is marked by the onset of constitutional symptoms. This usually occurs when the CD4 count declines to approximately 200 cells/μL. Here, the immune system cannot prevent opportunistic infections (OIs) and lymphomas from occurring due to the now low levels of CD4 cells. During this late phase of HIV, the VL also increases dramatically. Once an individual experiences an OI listed in Table 1.1[37], the individual is considered to be at an advanced stage of HIV, acquired immunodeficiency syndrome (AIDS). Once a person has reached this stage, in the absence of treatment, at some point they would inevitably die from their condition.

Table 1.1: World Health Organisation (WHO) clinical stage 4: AIDS-defining conditions

Clinical conditions	Further details
HIV wasting syndrome	>10% of body weight associated with either chronic diarrhoea or chronic weakness and fever for ≥1 month
Pneumocystis pneumonia	
Recurrent severe bacterial pneumonia	>1 month
Chronic herpes simplex infection	Orolabial, genital, anorectal, visceral at any site
Candidiasis/candida	Oesophagus, trachea, bronchi, lungs
Extra pulmonary tuberculosis	
Kaposi sarcoma	
Cytomegalovirus infection	
Central nervous system toxoplasmosis	
HIV encephalopathy	
Cryptococcosis, extra pulmonary	Including meningitis
Disseminated non-tuberculosis mycobacteria infection	
Progressive multifocal leukoencephalopathy	
Chronic cryptosporidiosis	With diarrhoea
Chronic isosporiasis	
Disseminated mycosis	
Recurrent non-typhoidal Salmonella bacteraemia	
Lymphoma	Cerebral, B-cell non-Hodgkin
Invasive cervical carcinoma	
Atypical disseminated leishmaniosis	
Symptomatic HIV-associated nephropathy	
Symptomatic HIV-associated cardiomyopathy	
Reactivation of American trypanosomiasis	

1.2 **Antiretroviral drugs for the treatment of HIV**

HIV is treated with antiretroviral drugs (ARVs) and the treatment regimen is referred to as antiretroviral therapy (ART). There are currently five main classes of ARV that act at different points in the HIV lifecycle:

- Nucleoside/Nucleotide Reverse Transcriptase Inhibitors (NRTIs)[38]
- Non-Nucleoside Reverse Transcriptase Inhibitors (NNRTIs)[38]
- Protease Inhibitors (PIs)[38]
- Entry/Fusion Inhibitors[39]
- Integrase Strand Transfer Inhibitors (InSTIs)[40;41].

1.2.1 **Brief history of HIV treatment**

The first ARV was the NRTI zidovudine (AZT), which was approved for the treatment of HIV in the US by the Food and Drug Agency (FDA) in 1987 following lower rates of OI and death compared with placebo in clinical trials[42]. In this period of monotherapy, the life-prolonging effects were only around 6-18 months[43], there were many serious adverse reactions (partly due to the very high doses used)[44], and studies reported the rapid emergence of drug-resistant mutations[45]. AZT was the only approved treatment for HIV until 1991 when didanosine (ddI) and zalcitabine (ddC) were licenced[46;47]. To overcome the development of drug resistance, combinations of two (both from the NRTI class at this time) were recommended, known as dual therapy.

The FDA approved the first PI, saquinavir, in 1995, which allowed for combination antiretroviral therapy (cART) for the first time, also known as highly active antiretroviral therapy (HAART). cART is typically defined as a treatment regimen containing at least three ARVs, which were initially two NRTIs and a PI. This is now commonly considered a regimen consisting of two NRTIs (the “backbone”) alongside a third drug from the PI, NNRTI or InSTI classes. cART has been recommended for treatment of HIV since 1996 when it was shown to be superior to mono or dual therapy[48-52]. Ritonavir (RTV)-boosted PIs combine a low dose of RTV at sub-therapeutic levels with a second PI to achieve higher sustained levels of the second PI. These regimens were used from around 2000[53], increasing the efficacy of the PI and allowing for less frequent dosing[54]. The introduction of cART revolutionised HIV treatment, and since 1996 there has been a sustained decrease in both morbidity and mortality[55;56]. The projected life expectancy for HIV infected individuals now approaches that of the general population in high-income countries[57] and HIV is often considered as a chronic, manageable condition rather than a terminal infection[55;58-60].

When cART was first introduced, individuals were taking up to 10 tablets every eight hours[61-63]. Alongside this very high pill-burden, individuals had strict dietary restrictions and suffered serious toxicities. Over time, with the introduction of new ARVs and changes to the dosing schedules for some of the existing regimens, the number of doses required per day and thus the number of pills was reduced. In 2006, atripla, the first combination pill for one pill once a day was approved[64]. Since then other single tablet regimens have been introduced including eviplera, stribild and triumeq. With the introduction of a wider choice of ARVs, treatment tolerability has improved. The main ARVs and co-formulations in current use are in Table 1.2[65].

As discussed above, early mono/dual NRTI regimens had inferior efficacy compared to cART. However, recent studies of modern, PI-based mono or dual ARV regimens have suggested they may have reasonable efficacy to cART for maintaining virological suppression, among individuals who have already achieved virological suppression[66-72] and as such may be a reasonable treatment option for specific groups[73]. Furthermore, there is evidence that these regimens are more cost-effective[68;74;75] and that NRTI-sparing regimens may avoid some of the NRTI-associated side effects (Table 1.2)[70;76;77].

Table 1.2: FDA approved HIV medicines

Drug Class	Drug name (acronym)	FDA Approval date	Recommended current dosing	Common side effects
NRTIs	Zidovudine (AZT, ZDV)	March 1987	1 BD	Nausea, vomiting, fatigue, anaemia, lipoatrophy, muscle pain
	Didanosine (ddI) [a]	October 1991	1 OD	Peripheral neuropathy, lactic acidosis, pancreatitis
	Stavudine (d4T) [a]	June 1994	1 BD	Peripheral neuropathy, lipoatrophy, lactic acidosis
	Lamivudine (3TC)	November 1995	1 or 2 OD	Peripheral neuropathy, hair loss
	Combivir (3TC/AZT) [a]	September 1997	1 BD	(See individual components)
	Abacavir (ABC)	December 1998	2 OD	Hypersensitivity
	Trizivir (ABC/3TC/AZT) [a]	November 2000	1 BD	(See individual components)
	Tenofovir disoproxil fumarate (TDF)	October 2001	1 OD	Kidney function, reduced bone mineral density
	Emtricitabine (FTC)	July 2003	1 OD	
	Kivexa (ABC/3TC)	August 2004	1 OD	(See individual components)
	Truvada (FTC/TDF)	August 2004	1 OD	(See individual components)
	Tenofovir alafenamide	April 2016	Only available in formulation	
	Descovy (FTC/TAF)	April 2016	1 OD	
NNRTIs	Nevirapine (NVP)	June 1996	1 OD or 1 BD	Rash, liver problems
	Delavirdine (DLV) [a]	April 1997	4 TTD	Rash, headache, nausea, diarrhoea, excessive tiredness
	Efavirenz (EFV)	September 1998	1 OD	Sleep disturbance, mood changes, rash, liver problems, lipid changes, kidney problems
	Etravirine (ETR)	January 2008	1 or 2 BD	Rash, nausea, liver problems
	Rilpivirine (RPV)	May 2011	1 OD	Depressive disorders, rash, nausea, liver problems
PIs	Saquinavir (SQV) [a b]	December 1995	2 BD	Lipid changes, lipodystrophy, diarrhoea, heart rhythm problems, liver problems
	Ritonavir (RTV) [c]	March 1996	Depends on PI that it is boosting	Nausea, vomiting, lipid changes

Drug Class	Drug name (acronym)	FDA Approval date	Recommended current dosing	Common side effects
	Indinavir (IDV) [a]	March 1996	2 BD	Urine crystals, kidney stones, hair loss, dry skin, frozen shoulder, jaundice, lipid changes, diarrhoea, lipodystrophy
	Nelfinavir (NFV) [a]	March 1997	5 BD	Diarrhoea, lipid changes
	Lopinavir/ ritonavir (LPV/RTV or LPV/r) [b]	September 2000	2 BD	Nausea, diarrhoea, lipodystrophy, lipid changes, heart disease
	Atazanavir (ATV)	June 2003	2 OD	Nausea, diarrhoea, lipodystrophy, jaundice
	Fosamprenavir (FPV) [b]	October 2003	1 BD	Nausea, diarrhoea, rash, lipid changes, lipodystrophy
	Tipranavir (TPV) [a b]	June 2005	2 BD	Nausea, tiredness, diarrhoea, lipodystrophy, lipid changes
	Darunavir (DRV) [b]	June 2006	1 OD	Nausea, diarrhoea, rash, lipodystrophy, lipid changes
	Atazanavir/ cobicistat (ATV/COBI)	January 2015	1 or 2 OD	(See individual components)
	Darunavir/ cobicistat (DRV/COBI)	January 2015	1 OD	(See individual components)
Fusion inhibitors	Enfuvirtide (T-20) [a]	March 2003	1 injection BD	Injection site reaction, bacterial pneumonia, allergy
Entry inhibitors	Maraviroc (MVC)	August 2007	1 OD	Rash, muscle and joint pain, dizziness, may affect heart
InSTIs	Raltegravir (RAL)	October 2007	1 BD	Nausea, rash, diarrhoea, headache
	Dolutegravir (DTG)	August 2013	1 OD	Sleep disturbance, mood changes
	Elvitegravir (EVG) [b]	September 2014	1 OD	
Pharmaco-kinetic Enhancers	Cobicistat (COBI) [c]	September 2014	1 OD	
Complete regimen [d]	Atripla (EFV/FTC/TDF)	July 2006	1 OD	
	Eviplera (FTC/RPV/TDF)	August 2011	1 OD	
	Stribild (EVG/COBI/FTC/TDF)	August 2012	1 OD	
	Triumeq (ABC/DTG/3TC)	August 2014	1 OD	
	Genvoya (EVG/COBI/FTC/TAF)	November 2015	1 OD	
	Odefse (FTC/RPV/TAF)	March 2016	1 OD	

[a] Withdrawn or no longer recommended in the UK; [b] need to be boosted with RTV; [c] now only used to boost drug levels of other drugs; [d] see the individual drugs in formulation for side effects; OD= once daily; BD= twice daily; TTD= three times daily.

1.2.2 **Surrogate markers for ART response**

Lower CD4 counts and higher VLs are strongly associated with increased risk of AIDS and death[78-83], particularly the CD4 count. Therefore, these are commonly used as surrogate clinical markers for response to ART.

The main marker of ART response is suppression of VL to levels below that which is quantifiable. The defined limit for virological suppression varies depending upon the lower limit of assay used. Since approximately 1999, the lower limits of VL assays have commonly been 40 or 50 copies/mL, though the most sensitive assays are currently able to measure as low as one copy/mL. Sometimes a single or confirmed VL <200 copies/mL is used as a marker of response to ART, in accordance with recommendations in the US to allow for variation between VL assays[84].

Once levels of viral replication have been suppressed, immune reconstitution usually occurs, with a corresponding increase in CD4 cell counts. The pattern most commonly seen is a rapid increase in the CD4 count in the first months of ART[85]. This is followed by a steady increase of approximately 50 to 100 cells/μL per year until a stable level is reached[86]. In the long-term, for many HIV-positive individuals, this level is above 500 cells/μL (i.e. represents a return to levels in the normal range)[87;88]. These improvements in CD4 cell counts have been shown to be a very good surrogate marker for immunological function, and therefore also for clinical response[89].

1.3 **Stages in the continuum of care and policies and recommendations in order to achieve them**

The continuum of care for HIV is a model describing the stages involved in the diagnosis and management of HIV, and includes a timely diagnosis, retention in care, receipt of appropriate antiretroviral treatment and achievement of a good treatment response. There are a number of stages across the care spectrum at which individuals can be ‘lost’ from the health system: testing for HIV, linkage to care, retention in care, initiation of treatment, and adherence to treatment.

Several bodies produce guidelines for HIV care. The World Health Organisation (WHO) makes worldwide recommendations on healthcare, including for treatment of HIV. The European AIDS Clinical Society (EACS) produce European guidelines for the treatment of HIV-infected adults. The British HIV Association (BHIVA) is a national advisory body on all aspects of HIV care. Clinical treatment guidelines for the UK have been written by BHIVA since the early 1990’s, and these include guidance on when to initiate ART and with which ARVs. The guidelines are accredited by the National Institute for Health and Clinical Excellence (NICE)[90].

1.3.1 **Diagnosis**

CD4 counts are useful markers of stage of HIV infection at the time of diagnosis. A timely HIV diagnosis is important for slowing the progression of HIV[91;92] and therefore improving prognosis[93-99], reducing onwards transmission[100;101] and reducing costs to health services[102;103]. Although several definitions have been proposed, late diagnosis is now generally defined by consensus as diagnosis with CD4 count <350 cells/μL and very late diagnosis as a CD4 count <200 cells/μL[104]. Individuals with delayed diagnosis continue to have a 10-fold increased risk of death in the year following diagnosis[105]. Even in high-income countries, late diagnosis of HIV remains prevalent[106-114]. Of concern, late diagnosis means that ART will necessarily be initiated at a CD4 <350 cells/μL. It is worth noting that time of diagnosis is not the same as time of infection. In fact, individuals may have a long time between infection and diagnosis for many reasons, including lack of symptoms, low perceived risk, fear of stigma, fear of positive result, and lack of health education.

1.3.1.1 ***Testing and screening policies in the UK***

Prior to 2001, HIV tests in the UK were primarily provided upon request of the individual in a genitourinary medicine (GUM) clinic. The National Strategy for Sexual Health and HIV then recommended that GUM clinics should offer an HIV test to everyone on an opt-out basis[115], and most now use this strategy. In antenatal settings, prior to 2000, the level of HIV testing was health-care worker dependent, however, the introduction of a universal opt-out system resulted in a vast improvement in antenatal testing rates and a large reduction in the proportion of undiagnosed HIV infections at delivery[116]. In the most recent BHIVA guidelines, published in 2008, universal HIV testing is recommended in: GUM or sexual health clinics, antenatal services, termination of pregnancy services, drug dependency programmes, and healthcare services for those diagnosed with tuberculosis, hepatitis B, hepatitis C and lymphoma[117]. A HIV test should also be considered for all individuals registering at a general practice and all general medical admissions where diagnosed HIV prevalence in the local population exceeds two in 1000 population. HIV testing is recommended to be routinely performed among blood donors, dialysis patients, and organ transplant donors and recipients[117].

In terms of testing frequency, repeat HIV tests are required for individuals who have tested HIV negative but where a possible exposure has occurred within the window period[117]. BHIVA guidelines recommend that MSM and PWID test for HIV annually, or more frequently if they are likely to be in primary infection or are still having high-risk exposures. Women attending antenatal clinics should be re-offered an HIV test on two additional occasions during pregnancy if it is declined upon booking.

In April 2013, the management of HIV prevention services, transferred from the NHS to local authorities. The London HIV Prevention Programme (LHPP) is a joint commissioning of key HIV prevention services by all 33 London councils[118]. This is a significant challenge since HIV prevalence exceeds two in 1000 population in 32 of 33 London boroughs, so these are therefore considered high prevalence areas. The LHPP aims to increase the frequency of HIV testing, promote consistent condom use and safer sexual behaviours, in pursuit of which they have gained funding for condom distribution and for London-wide testing campaigns.

Rapid (point-of-care) HIV testing involves an HIV test which can be conducted in a doctor's office or community setting and does not need to be sent to a laboratory to get the results. Test results can usually be given in 20-30 minutes which is their major benefit over general HIV tests. However, BHIVA recommend that all positive results must be confirmed by serological tests as there will be false positives, particularly in lower prevalence environments[117]. This is because rapid HIV tests have been found to have a lower sensitivity and specificity[119]. Postal and self-testing allow the individual the privacy and convenience of testing for HIV from home. While the individual can conduct both of these types of tests, postal tests need to be sent off to a laboratory to be tested whereas the individual can read self-test results themselves within 15-20 minutes. Postal tests have always been legal in the UK, but self-testing kits became legal in the UK in April 2014. Rapid testing, postal testing, and self-testing are all ways in which HIV testing has become more easily accessible over time, which studies have shown to be associated with reduced HIV transmission and an increase in retention in care[120-123].

1.3.2 **Initiation of ART**

As is the case for many chronic conditions, for PLWH worldwide, poor access to healthcare and treatment is a significant problem. In settings without universal free access to care there may be financial barriers to accessing ART[124]. Other barriers to starting ART include lack of health literacy, perceptions of discrimination, fear, language barriers and lack of trust in the healthcare system.

1.3.2.1 ***When to start***

Lower CD4 count and higher VL at the time of initiating ART are strongly predictive of longer time to achieving virological suppression[125-128], lower short-term CD4 counts[127], lower likelihood of CD4 counts returning to normal levels[129], and faster progression to AIDS and death[130;131]. Even among those with a timely diagnosis, delayed HIV treatment initiation is associated with poorer health outcomes[132].

Recommendations of when to start by the WHO, EACS, and BHIVA have varied considerably over time. Regardless of CD4 count, individuals have been recommended to initiate ART upon onset of clinical symptoms. However, for asymptomatic individuals, CD4 count has generally been the determining factor for when to initiate treatment. Until 2015 EACS and BHIVA both recommended starting ART before the CD4 count fell below 350 cells/μL[133] and WHO recommended starting when the CD4 count is below 500 cells/μL[134]. However, the Strategic Timing of Antiretroviral Therapy (START) randomised controlled trial (RCT) demonstrated that starting ART with a CD4 count of above 500 cells/μL is superior with respect to clinical endpoints than waiting for the CD4 count to reach 350 cells/μL[135]. Following these results, WHO, EACS and BHIVA have all since removed the CD4 threshold for recommending when to initiate ART[136;137]. This is called the "test and treat" strategy, because individuals are now recommended to start ART immediately or as soon as they are ready[138;139].

Initiating ART in primary infection was recommended to occur only within the setting of clinical trials for a number of years in the UK[133;140-143]. Studies have shown that starting treatment in primary infection can improve immune control[144], however, long-term adherence, potential toxicity and development of resistance were additional considerations that meant that treatment was recommended to be deferred[124;129-132]. More recently, studies have shown improvements in long-term immunological and virological outcomes among those initiating ART in primary infection[145]. Since 2015 initiation of treatment as soon as possible has been recommended by BHIVA for individuals in primary HIV infection[136].

1.3.2.2 ***What to start***

The choice of which ARVs should be included in an individual's first-line regimen is dependent upon possible side effects, potential for drug interactions, drug resistance, health of the individual, convenience and cost. The recommendations of which ARVs to include in first-line regimens have changed over time so the most commonly used regimens have also changed over time.

In 2000, BHIVA recommended that ART-naïve individuals start cART containing two NRTIs and either a PI, an NNRTI, or a third NRTI[140]. In the guidelines published in 2003 however, triple NRTI regimens and regimens including PIs not boosted with Ritonavir were no longer recommended[141]. A regimen composed of two NRTIs and an InSTI was first recommended in BHIVA guidelines in 2012 when Raltegravir was included as a preferred third agent[133]. In the 2015 guidelines, BHIVA recommended that ART-naïve individuals start cART containing two NRTIs (preferred: TDF FTC;

alternative: ABC 3TC) and either a RTV-boosted PI (ATV/r or DRV/r), an NNRTI (preferred: RPV; alternative: EFV), or an InSTI (DTG, RAL, or EVG/COBI)[136]. Efavirenz was changed from a preferred NNRTI option in the 2012 guidelines to an alternative option in the 2015 guidelines, since other ARVs, including Dolutegravir, have demonstrated superiority[146]. This was mainly due to higher rates of discontinuation among individuals on Efavirenz due to adverse events[147;148]. The recommendations of what regimen to start initial HIV treatment with vary depending on factors including diagnosis of Hepatitis B or C (HBV or HCV), other chronic conditions, and pregnancy.

1.3.2.3 ***Treatment as prevention***

Treatment as Prevention (TasP) is the term used to describe interventions used to reduce the rate of transmission of HIV. The idea of this method is to reduce an individual's VL to levels at which they are less likely to be infectious – since VL is the most important factor in risk of HIV transmission as mentioned in Section 1.1.2.1 The results of the HPTN 052 and PARTNER studies provided evidence that individuals with a suppressed VL had a very low risk of transmitting HIV through sexual intercourse (anal or vaginal)[149;150]. The new recommendation to treat all individuals newly diagnosed with HIV with ART as soon as possible (see Section 1.3.2.1) both aims to improve the individual's prognosis and to reduce the risk of onwards transmission. Prevention of mother-to-child transmission (PMTCT), post-exposure prophylaxis (PEP) and pre-exposure prophylaxis (PrEP) are also methods which use ART to prevent transmission.

PMTCT is the treatment of a women with ARVs during and after pregnancy, regardless of whether they would usually have been recommended to initiate ART, with the aim of preventing vertical transmission to their child. PMTCT has been used since the mid-1990s and has been found to reduce the risk of transmission to the child by up to 95%[151]. As a result, vertical transmission in the UK has substantially declined over time[152].

PEP is a short course of ARVs given to individuals who have had recent exposure to HIV. PEP has been used for health-care workers occupationally exposed to HIV infection since 1998[153]. More recently, PEP has been used to treat individuals who may have had exposure to HIV in a single event (e.g. unprotected sex)[154]. To be effective PEP must be taken as soon as possible after the exposure and most guidelines recommend that it is taken within 48 hours. The first UK guidelines on PEP were published in 2006, these stated that PEP was recommended for individuals who:

had had anal or vaginal sex with an HIV positive individual, or had receptive anal sex with a person of unknown HIV status but from a group or area of high prevalence[155].

PrEP is the use of ARVs by HIV negative individuals to prevent HIV infection prior to potential exposures[156]. Studies have shown that when adhered to as prescribed, the risk of infection when using PrEP is near-zero[157;158]. Initially it was only recommended for key affected populations, such as MSM or PWID, but in 2015 WHO recommended that PrEP be offered as a choice to all individuals at high-risk of HIV infection (e.g. partners of PLWH)[159]. In 2016, BHIVA recommended that PrEP be offered to: (i) MSM, trans men and trans women who are engaging in condomless anal sex; (ii) HIV-negative partners who are in serodifferent heterosexual and same-sex relationships with a HIV-positive partner whose viral replication is not suppressed; and (iii) other heterosexuals considered to be at high risk[160]. Although, PrEP can be accessed under the NHS in Scotland and Wales, this is not yet the case in England, except for for participants in the IMPACT trial[161].

1.3.3 **Response to ART**

Despite the hugely successful impact of ART on the prognosis for PLWH, there is yet no cure. The Strategies for Management of Antiretroviral Therapy (SMART) study published in 2006 found that episodic ART guided by CD4 count significantly increased the risk of opportunistic infections or any-cause mortality compared to continuous ART[162]. Furthermore, despite being the purpose of the CD4 count-guided treatment interruptions, the risk of ART-associated adverse events (see Section 1.3.3.1) was not reduced in the SMART study. Thus, ART is a lifelong commitment, as it is generally not recommended to take treatment interruption or 'holidays.' Successful long-term virological suppression on ART is therefore critical[163-170]. The most common reasons for treatment failure are drug toxicities, drug-resistance, and ART non-adherence, all of which are closely linked[171-174].

1.3.3.1 ***Drug toxicities***

Owing to the success of cART in improving life expectancy[57], PLWH are taking ARVs for a longer period of time, and therefore they potentially have to deal with side effects of ARVs (Table 1.2) in the long-term. Side effects, otherwise known as adverse effects or toxicities, are not uncommon with ARVs. Use of certain ARVs has been shown to be associated with cumulative long-term toxicities such as cardiovascular disease (diseases of the heart and circulation)[175-181], nephrotoxicity (kidney toxicity)[182-185], and lactic acidosis (inadequate clearance of lactic acid from the blood)[186-188]. Early treatment regimens came with a lot of associated toxicity, however, through the introduction of new, more tolerable ARVs there has been a reduction in incidence of

some toxicities, such as lipodystrophy (fat loss or redistribution). Toxicities may make it difficult for individuals to take their treatment and they may need to change their ART regimen[174;189;190].

1.3.3.2 ***Drug resistance***

HIV is a member of the retrovirus family, which inherently have a high mutation rate due to the lack of "proof-reading" ability[191;192]. Wild type virus, which is susceptible to all antiretroviral drugs, is usually the dominant type as it has the highest replicative capacity. However, other virus types are preferentially selected, despite having lower viral fitness in some situations. Drug resistant virus refers to HIV strains that contain mutations that confer resistance to antiretroviral drugs, which in turn leads to the replication of HIV even in the presence of ART. Antiretroviral drug resistance most commonly occurs amongst people with incomplete virological suppression on ART, for example during periods of moderate adherence[193]. Although each antiretroviral has its own specific resistance profile, there are a number of mutations that historically conferred resistance to a whole drug class[194;195]. This in turn can lead to a higher cost or less effective second/third-line regimens and transmission of drug-resistant strains of HIV. However, the risk of exhaustion of treatment options due to resistance has decreased over time with the introduction of more ARVs which have higher thresholds before resistance occurs, and improved resistance profiles which remain active even in the presence of mutations that would have previously conferred class-wide resistance[196]. In high income countries, the prevalence of transmitted HIV drug resistance has stabilised in recent years[197;198].

1.3.3.3 ***ART non-adherence***

Non-adherence to ART has emerged as the major determinant for treatment success[199]. Non-adherence covers three areas: dose non-adherence (missing ART doses), schedule non-adherence (not taking doses at the correct time) and instruction non-adherence (not taking doses under the correct conditions e.g. with food). Non-adherence may occur due to individual choice (for example due to high levels of toxicity or life events), lack of comprehension of treatment schedule, or forgetting. Non-adherence to ART is a significant predictor of virological non-suppression and treatment failure[171;173;199;200]. Poor adherence can also lead to the development of drug resistance[201-203] and the subsequent increased risk of onward transmission[202;204].

Adherence to ART can be measured in a number of ways: self-report, Medical Event Monitoring Systems (MEMS) caps (counting the number of times a pill bottle is opened), pill-count (number of pills left is counted), prescription coverage (time covered by prescription), clinician report, or a combination of these. Self-report is the

most commonly used measure since it is the easiest to obtain and least costly measure. Despite the frequent use of self-report to define adherence, the lack of standardisation of questions (with regard to how many missed doses count as poor adherence and over what time period they consider) means that even among studies using self-reported adherence measures it is difficult to make comparisons between them[205]. The main disadvantage of self-reported variables is that they may be more subject to error and bias. For example, individuals may not remember all missed doses, particularly over longer periods, or may tend to over-estimate adherence due to social desirability bias – the tendency of respondents to answer questions in a manner that they believe will be viewed favourably by others. It is difficult to accurately capture adherence to treatment by any one measure[206;207], however, collecting multiple measures may be impractical in a clinical setting.

1.4 **The current HIV epidemic in the UK**

1.4.1 **The number of people living with HIV in the UK**

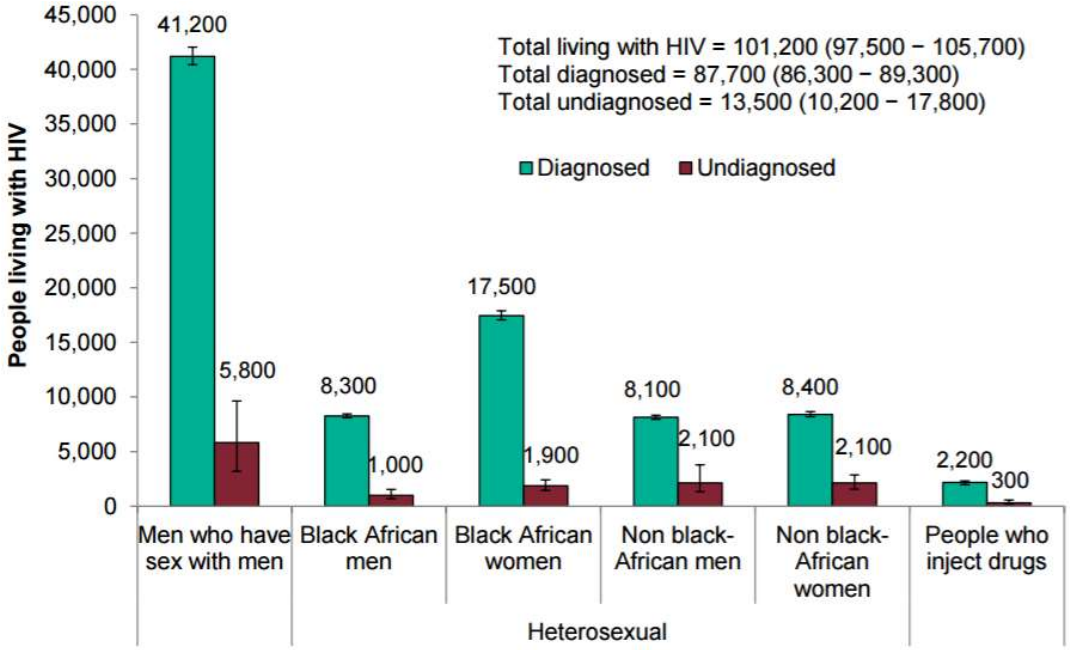
In the UK in 2015, there was a rate of new diagnosis of 11.4 per 100000 people[208]. Of the countries in Western Europe, the UK has the highest rate of HIV per head population, with the exception of Luxembourg[209]. In 2015 there were an estimated 101200 PLWH in the UK (95% credible interval (CrI): 97500, 105700), of whom, 18100 (95% CrI: 10200, 17800) or 13% (95% CrI: 10%, 17%) were estimated to be unaware of their HIV status[208].

1.4.2 **Demographics of people living with HIV in the UK**

1.4.2.1 ***HIV prevalence in the UK***

In 2015, the overall HIV prevalence was estimated to be 1.6 per 1000 population (95% CrI: 1.5, 1.6) among all ages and 2.1 per 1000 population (95% CrI: 2.0, 2.2) among individuals aged 15-74 years (Figure 1.1)[208]. When considered in men and women separately, the prevalence was 2.3 per 1000 (95% CrI: 2.2, 2.5) among men and 0.98 per 1000 (95% CrI: 0.95, 1.02) among women[208]. Women account for about a third of individuals infected with HIV in the UK[210]. MSM and black African heterosexuals are disproportionally affected by HIV: in 2015 the prevalence per 1000 population was 58.7 (95% CrI: 51.2, 88.0) for MSM, 22.2 (95% CrI: 21.3, 23.6) for black African men and 42.6 (95% CrI: 41.0, 44.3) for black African women[208].

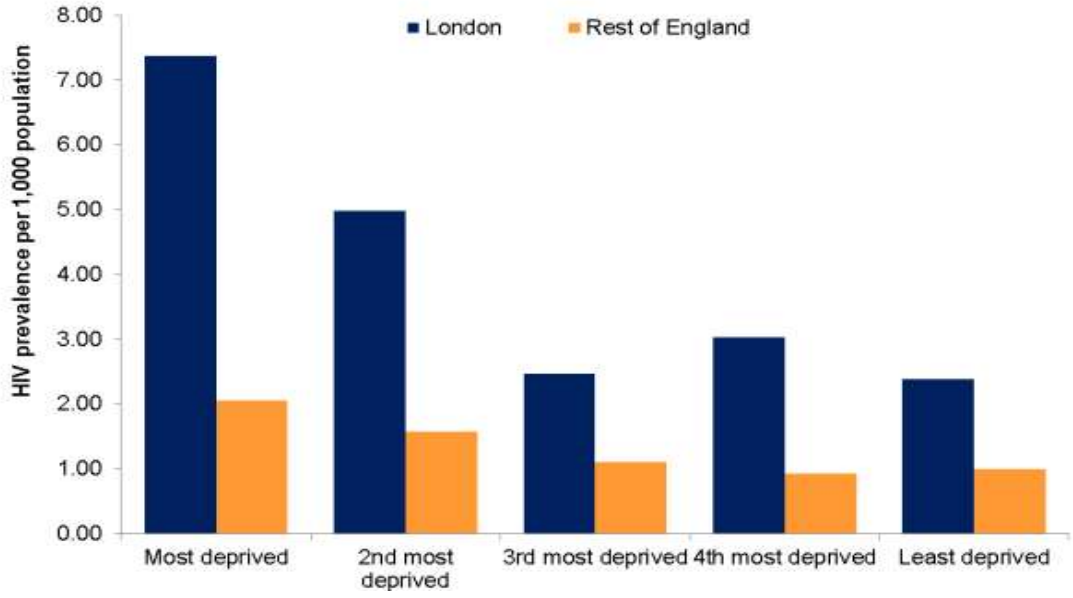
Figure 1.1: Estimated number of people living with HIV of all ages (diagnosed and undiagnosed) using the MPES model: UK, 2015



MPES=Multi-Parameter Evidence System

It has been acknowledged that, similar to other chronic conditions, socio-economic deprivation is associated with a greater likelihood of being infected with HIV[211]. In London in 2013, it was estimated that the HIV prevalence among adults aged 15-59 years was 7.4 per 1000 population in the most deprived areas compared to 2.4 in the least deprived areas (Figure 1.2[105]).

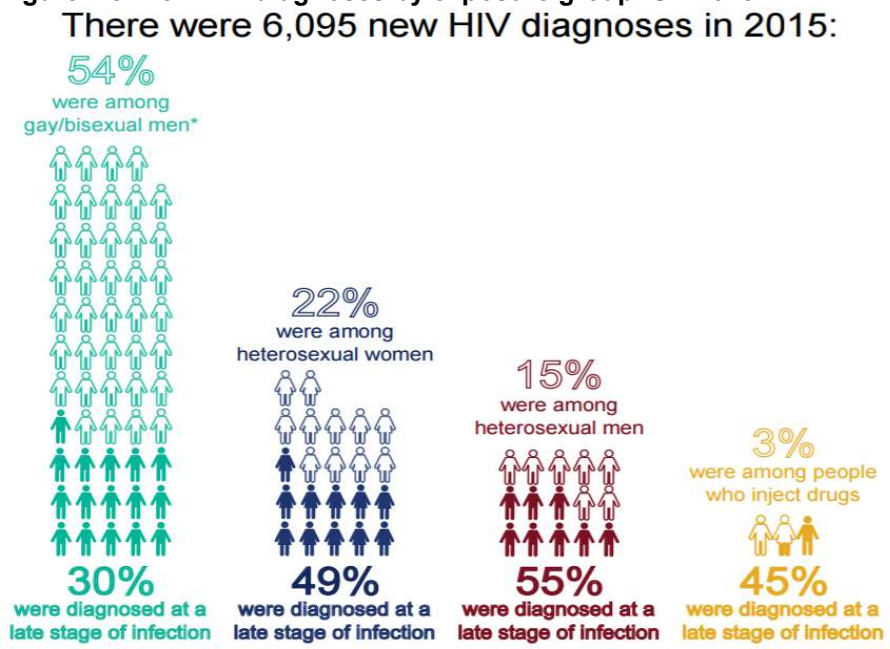
Figure 1.2: Prevalence of adults aged 15-59 years diagnosed HIV infection by index of multiple deprivation (IMD): England, 2013



1.4.2.2 ***New HIV diagnoses in the UK***

Of a total of 6095 people diagnosed with HIV in the UK in 2015, 3320 (54%) men acquired HIV through sex with men, 1010 (15%) men acquired HIV through heterosexual sex, 1350 (22%) women acquired HIV through heterosexual sex, and 210 (3%) acquired HIV through IDU (Figure 1.3)[208].

Figure 1.3: New HIV diagnoses by exposure group: UK 2015



* Gay/bisexual men also includes gay/bisexual men who have injected drugs

Over time, there has been a resurgence in transmission among MSM[212;213], who represented over half of all new diagnoses in 2015. The high levels of new HIV diagnoses among MSM are a result of both increased levels of HIV testing and ongoing high rates of transmission[208]. However, there is some indication from very recent data that the rate of transmission amongst MSM may be declining, perhaps due to PrEP, TasP and other behavioural changes[214]. The number of new diagnoses among heterosexuals has almost halved in the last decade (4340 in 2006 vs. 2360 in 2015), mainly due to fewer reports among African-born men and women, reflecting changing migration patterns[208]. Since the inception of the needle exchange program, transmission by IDU has decreased and remained at low numbers[215;216], although there was a notable increase between 2014 and 2015 (160 vs. 210) associated with an HIV outbreak among people who inject drugs (PWID) in Glasgow[208]. Similarly MTCT has been decreasing due to routine antenatal testing[217-219] and effective interventions such as avoidance of breastfeeding[220]. Although in the early stages of the epidemic, a number of people were infected by exposure to infected blood products, since 1985 blood has been screened for HIV in the US, Canada, and Europe[3], and therefore acquisition of HIV via this route is extremely rare. Overall, new

diagnoses in the UK are declining, however, the beneficial impact of HIV treatment contributes to the continuing rise in the number of PLWH[105].

1.4.2.3 ***Late HIV diagnoses in the UK***

Late diagnosis of HIV remains a challenge in the UK, with 39% of people newly diagnosed with HIV in 2015 having a CD4 count <350 cells/μL and 22% with a CD4 count <200 cells/μL[208]. Figure 1.4 shows that in 2015, a greater proportion of women compared to men, older individuals, individuals of black ethnicity, heterosexual men and women compared to gay/bisexual men, and individuals living outside of London were diagnosed late[208]. The proportion of individuals diagnosed late had declined from 56% in 2006 to 39% in 2015 and had declined across all HIV exposure groups, however, the decline was largest among heterosexual women (from 64% to 49%), mainly due to the antenatal screening programme and changing migration patterns[208]. Figure 1.5 shows that the one-year mortality rate among individuals diagnosed with a CD4 count <350 cells/μL was 31.5 per 1000 compared to 3.6 per 1000 among individuals diagnosed with a CD4 count ≥350 cells/μL[208]. Mortality rates were highest among men compared to women, individuals over 50 years old, individuals of other ethnicity compared to white or black ethnicity, and PWID (Figure 1.5).

Figure 1.4: Proportion of adults diagnosed late (CD4 count <350 cells/µL within three months of diagnosis) by demographic factors: UK, 2015

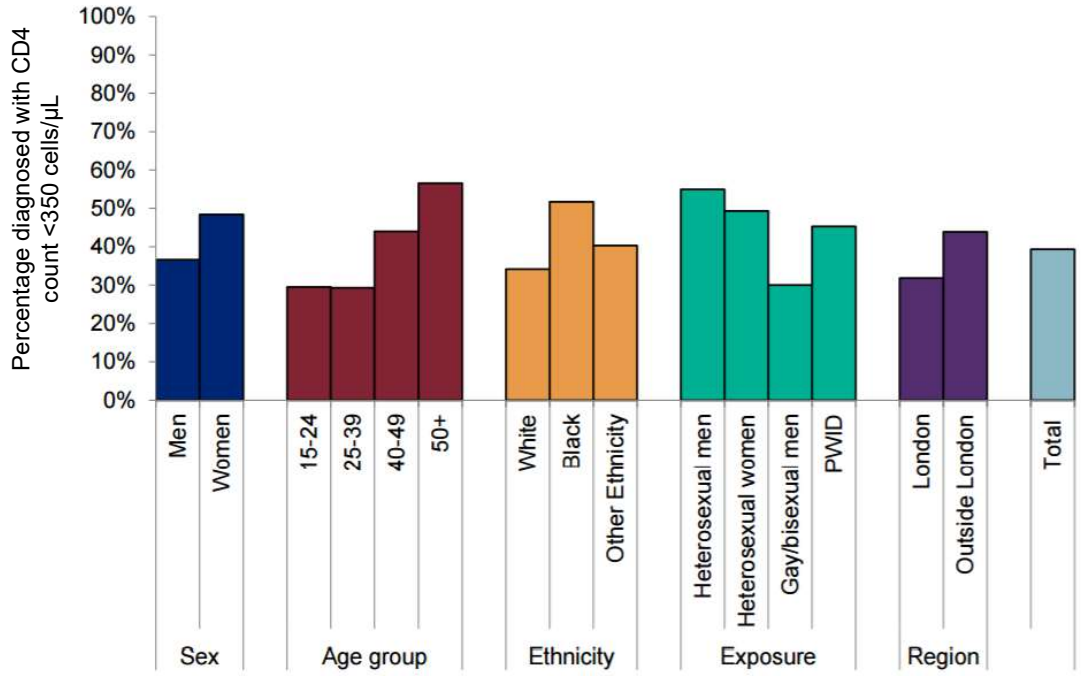
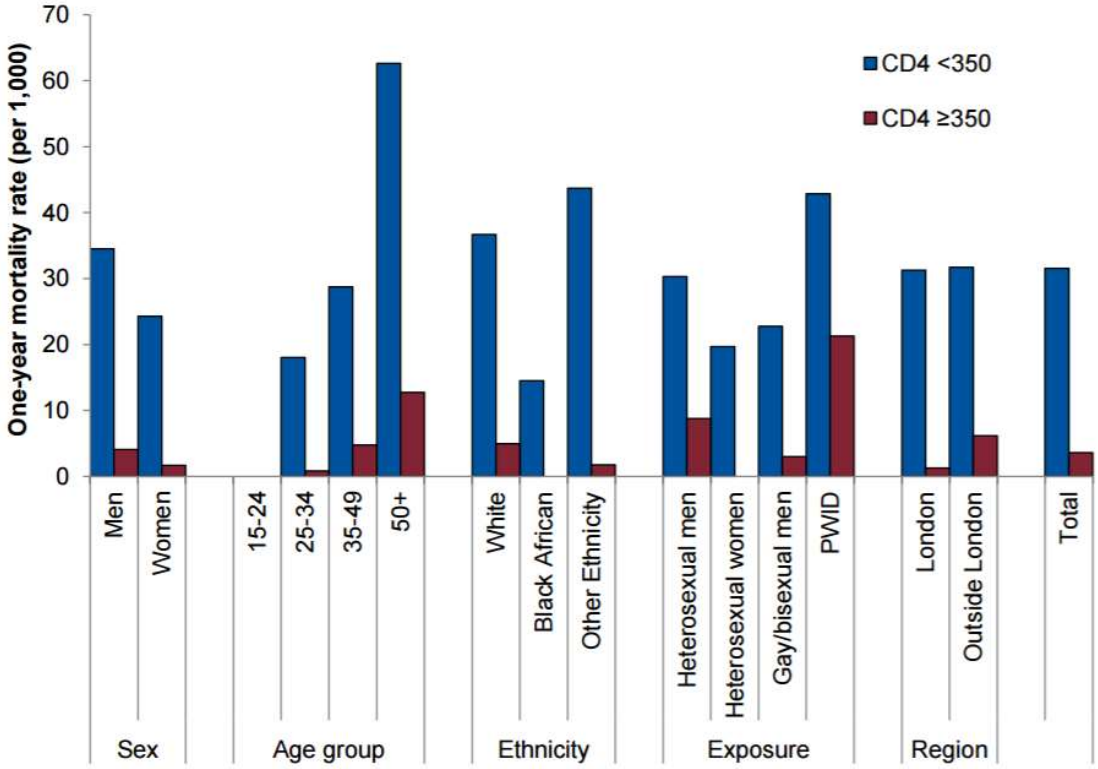


Figure 1.5: One-year mortality rates among adults newly diagnosed with HIV by CD4 count at diagnosis: UK, 2014

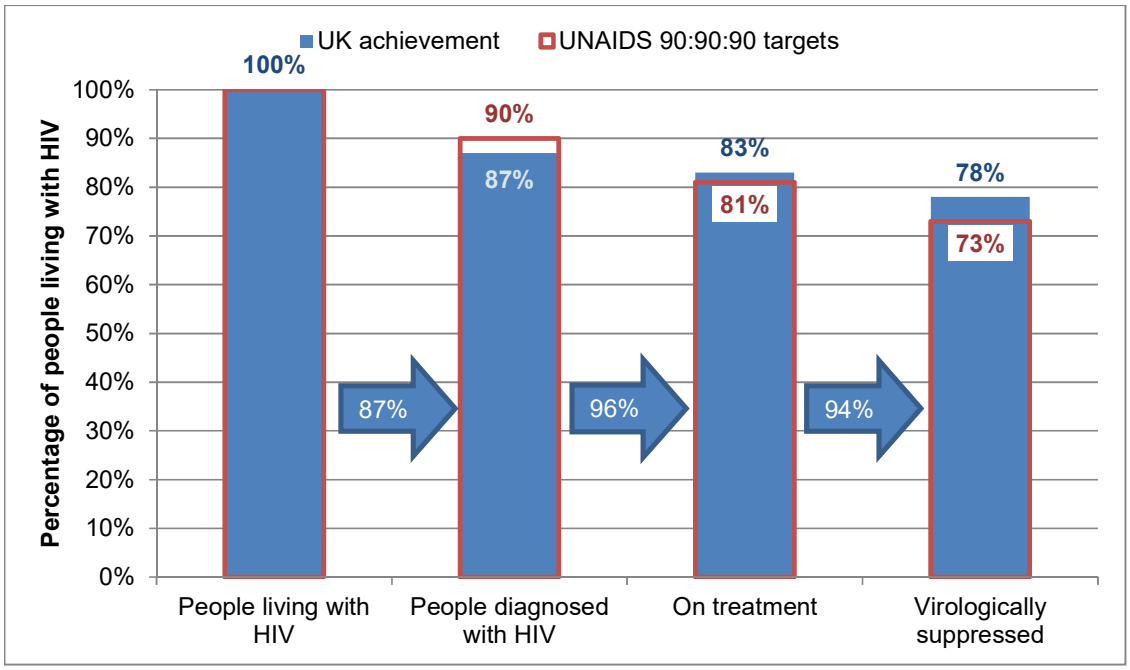


1.5 **The UK HIV care continuum: comparison to UNAIDS targets**

In 2014, UNAIDS introduced the "90-90-90" targets in terms of the HIV care continuum[221]. They proposed that by 2020: 90% of PLWH will be diagnosed, 90% of people HIV-diagnosed will be on sustained ART, and 90% of those receiving ART will have a suppressed VL. If these targets are achieved, then 81% of all PLWH will be on treatment and 73% will have an undetectable VL. Meeting this target would both improve the prognosis for PLWH and, modelling studies have suggested, potentially end the epidemic spread of HIV by 2030[221].

Among the estimated number of people living with HIV in the UK in 2015, 87% were HIV-diagnosed, 83% were on treatment and 78% were virologically suppressed[208]. Figure 1.6 shows these percentages by the blue bars, and the blue arrows denote the percentage of individuals at the stage before the arrow which have reached the subsequent stage (e.g. 94% of individuals on ART were virologically suppressed). The red bars in Figure 1.6 show the three UNAIDS targets. The UK has not yet reached the first UNAIDS target, having 90% of people living with HIV diagnosed, however, the second two targets have already been met and surpassed. Despite the progress towards meeting the 90:90:90 targets to date, the persisting high levels of HIV transmission and late diagnosis remain a concern in the UK[208].

Figure 1.6: UK HIV care continuum 2015: progress against UNAIDS 90:90:90 targets



1.6 Sex, gender and sexual orientation: differences in health outcomes and HIV outcomes in particular

1.6.1 Sex, gender, sexual orientation and health inequalities

There is evidence that men and women have differing health outcomes via biological mechanisms, including susceptibility to a number of conditions, from migraines to multiple sclerosis[222-226], and pharmacokinetic differences (because of differing gastrointestinal functioning, BMI, metabolism etc.)[227-230]. At a global level, women have a higher life expectancy than men, however, on average women have less years of "healthy life"[231]. This differs greatly by country; in those with less social discrimination, women's life expectancy is higher[232]. This difference in life expectancy is therefore unlikely to be because of biological sex alone but also differences in lifestyle and behavioural factors between men and women. Health inequalities reflect both biological sex differences and socially constructed gender differences and their interaction[233]. Some examples of where gender plays a role in health outcomes include: greater reporting of anxiety and depression among women despite no evidence that they are constitutionally more susceptible[234], masculine stereotyping making men more reluctant to access healthcare[235], women being less likely to receive social support and hence experiencing poorer positive coping[236], and men's greater partaking in risky behaviours such as smoking[237].

Differences in health outcomes by sexual orientation are not generally considered, except in the case of sexually transmitted infections (STIs) and mental health. Among men, reported STI acquisition has been found to be associated with increasing numbers of male sexual partners[238]. Men who self-identify as gay or bisexual are at six-fold increased risk of an STI diagnosis compared to self-identifying heterosexual men[239]. Among women however, studies have reported that self-identifying bisexual women have the highest risk of an STI diagnosis, followed by heterosexual women, and then lesbian women[240]. Multiple studies have also found differences by sexual orientation in the prevalence of mental health problems, i.e. MSM have been found to be at increased risk of mental health problems compared to men who have sex with women (MSW)[241-244].

1.6.2 Biological sex differences in HIV-related outcomes

Studies have previously considered whether there are biological differences in HIV-related outcomes by sex. There is evidence that women are more likely to acquire HIV per heterosexual act[3;20], they are more likely to be diagnosed during routine testing mainly due to routine opt-out antenatal testing[217-219;245], they have a higher CD4 count on average before HIV infection[22;246-249] and at seroconversion[250-252], and are at

increased risk of adverse reactions to ARVs[253] compared to men. There is also evidence of differences in pharmacokinetics and pharmacodynamics for ARVs[254]. More recently, there has been a greater focus on behavioural gender based differences in HIV-related outcomes.

1.6.3 **Non-biological gender differences in HIV-related outcomes**

HIV has similarities to several diseases, disorders and conditions, for example rheumatoid arthritis, asthma, and diabetes, in that they require long-term treatment adherence to avoid disease progression and ultimately mortality[255]. Several studies of rheumatoid arthritis[256-259], asthma[260-263], and diabetes[264-266] have observed poorer prognosis and increased risk of morbidity among women compared to men. Thus, it is possible that gender disparities would also be apparent for HIV treatment response. HIV differs to these conditions in that: infection is mainly acquired through sexual intercourse or intravenous drug use (IDU)[7;9]; individuals are infected at any age rather than predominantly among older individuals[267]; it disproportionately affects certain socio-demographic groups such as migrants and MSM; and the stigma attached and thus possible difficulties with disclosure[255;267;268]. Therefore, gender may affect responses to treatment differently for HIV.

In many studies investigating gender effects in HIV prognosis, MSW have been grouped with MSM and compared to women. This approach does not consider the differences between these two male groups. MSW are more often migrants than MSM[269;270], and more often have poorer SES[271]. Additionally, although there is some evidence that MSM are at increased risk of sexually transmitted infections (STIs)[272;273] and mental health problems[274-276], particularly men who self-identify as gay or bisexual[277], this group has been found to be more likely to test for HIV compared to self-identifying heterosexual men[278]. This means that MSM and MSW may have very different health profiles. This separation of men into whether they have sex with men or women would not be a reasonable consideration for women, since sexual HIV transmission between women is very rare.

One could consider comparing MSM with a single group of heterosexual men and women; however, there are also a number of reasons to consider women separately. There are known gender differences in utilisation of healthcare services and reporting of symptoms for other common diseases[279;280] which could also be apparent for HIV and lead to differences in response to treatment. Pregnancy affects the timing for ART initiation and which regimen is started[281], which may in turn affect subsequent response to ART[282]. Similarly, as women are more often the primary caregiver for children, the effect of having children is more likely to affect HIV-related outcomes and

adherence of women compared to men. However, in HIV-positive populations in high-income settings MSW often have greater similarities with respect to culture, demographics and SES with women than with MSM[283]. This suggests that, when assessing HIV-related outcomes, there are essentially three separate gender/sexual orientation groups that should be considered, rather than binary gender (see Chapter 2 for a full review of the literature).

1.7 **Socio-economic status: differences in health outcomes and HIV outcomes in particular**

SES is the position of individuals in society, based on a combination of occupational, financial and educational criteria. Less frequently, housing status, literacy or cultural characteristics may be used as indicators of SES[284]. Alternatively some studies consider neighbourhood-level measures using area-based deprivation as a marker for individual-level SES[285]. Individuals with higher SES might be thought of as having greater access to desired resources such as material goods, money, friendship networks, and educational opportunities. The terms “socio-economically disadvantaged” and “socio-economically deprived” are commonly used to describe individuals with limited access to these resources.

1.7.1 **Socio-economic status and health inequalities**

SES encompasses a range of indicators that have been identified as key to inequalities in health[286-288]. SES is a determinant of health predominantly through three pathways: access to healthcare, environmental exposures and health behaviour[289]. The extent that SES affects incidence and prognosis of ill health and chronic diseases is likely to differ between different healthcare settings. Although some settings, such as the US, have a reliance on ability to pay for healthcare and treatment, the UK has a national healthcare system so that access to healthcare and treatment is universally free at the point of care. However, ability to pay is by no means the only barrier to good health among individuals of lower SES: other barriers may include poorer health literacy (ability to read and comprehend medical information)[290-295], riskier or less healthy lifestyle[296-301], and fewer resources to facilitate access to healthcare (e.g. transport)[302]. There is evidence of an association between socio-economic disadvantage and poorer health across diverse health outcomes, ranging from the incidence of relatively minor illnesses such as headaches[303;304], to chronic conditions such as diabetes[305-307].

Despite universal healthcare coverage in the UK, various aspects of healthcare including longer hospital waiting times and longer wait for referral[308;309], and reduced access to health screening[310], healthcare[311] and needed surgery[312] have been found to be associated with poorer SES. Socio-economic factors such as social deprivation, lower income and education, have also been found to be associated with delayed diagnosis and poorer prognosis for a number of diseases, including cancer and chronic conditions such as diabetes and cardiovascular disease[305;313-318].

1.7.2 **Socio-economic differences in HIV-related outcomes**

As shown in Section 1.4.2.1 , there is a higher prevalence of HIV diagnoses in the most socio-economically deprived areas of the UK compared to the least deprived areas, particularly in London. Socio-economic disadvantage has been found to be associated with riskier sexual behaviours[319-322], which may partially explain the disproportionate amount of individuals of lower SES infected with HIV[7]. The demographic correlates of SES may also contribute to the association between SES and HIV prevalence.

1.7.3 **Correlation between socio-economic and demographic factors**

The HIV-positive population in the UK is made up of distinct demographic groups. For example, the majority of women and heterosexual men living with HIV are of black African ethnicity, whereas among MSM most individuals are of white ethnicity[208]. This means that studies considering gender differences in HIV outcomes are often likely concurrently examining differences by gender, ethnicity, culture and socio-economic background. The correlation between SES, ethnicity and route of transmission in particular means that the studies aiming to look at one of these factors are often comparing all at once. Therefore, when evaluating differences between demographic groups, it is important to consider these other factors, including SES. The extent to which differences in prognosis between demographic sub-groups can be explained by SES requires investigation.

1.8 **Summary**

In the UK, treatment outcomes are improving such that HIV is now considered a chronic but manageable condition. However, improvements may not have been experienced equally throughout the HIV-positive population. Disparities may occur between different demographic and socio-economic groups at various stages of the care continuum, including diagnosis and response to treatment. The specific aims and

objectives of this thesis are displayed in Chapter 3, following a literature review in Chapter 2.

Chapter 2 Literature review: gender/sexual orientation, socio-economic status and HIV treatment outcomes

2.1 Objectives

In this chapter, I address three questions among people with HIV and prescribed ART in high-income settings: (i) what evidence is there for an association between gender/sexual orientation and response to ART? (ii) what evidence is there for an association between SES and response to ART?; (iii) is there any evidence that observed differences in treatment responses according to gender/sexual orientation can be explained by differences in socio-economic circumstances, and vice versa? Three outcome measures are considered: (i) virological response (ii) immunological response (as measured by CD4 count) and (iii) ART non-adherence. As this thesis focusses on the UK setting, I only consider studies conducted in high-income countries, as they are likely to have similarities to the UK that mean that the results will be generalisable to some extent.

2.2 Methods

2.2.1 Overview

In Section 1.6.3 I showed that there were three main groups when considering gender differences, as it is very difficult to separate gender and sexual orientation as explanatory variables in the context of HIV. Thus, I began this chapter by presenting the results of my first systematic review, which summarised the literature on the association between gender/sexual orientation and ART response. However, since many studies have included gender as a covariate rather than gender/sexual orientation, I first gave an overview of studies that have considered the association between gender and HIV treatment outcomes without further sub-categorisation of the male group.

The effect of SES on ART response was the second focus of this thesis. Therefore, I conducted a second systematic review of the association between socio-economic factors and response to ART.

As discussed in Section 1.7.3, in the setting of HIV, demographic factors (particularly gender, sexual orientation and ethnicity) and SES are frequently interrelated in high-income countries[323;324]. Lower SES is strongly associated with a greater prevalence of

HIV infections particularly amongst MSW and women[320], thus there will be a wider distribution of SES among these individuals compared to MSM[136]. In order to understand the drivers of any potential gender/sexual orientation or SES inequalities in ART response, and in turn to help identify potential interventions to reduce them, I investigated evidence of the extent to which differences in treatment outcomes by gender/sexual orientation can be explained by SES, or vice versa. For this, I considered the studies identified by the two systematic reviews that included both gender/sexual orientation and SES in multivariable models.

There are several other potential mediators of the association of gender/sexual orientation and SES with treatment outcomes. Therefore, finally, I also looked at any other factors considered by any of the studies identified in the literature reviews that may explain gender/sexual orientation or SES differences in HIV-treatment outcomes. The primary potential mediator I considered was adherence, when it was considered as a covariate in models with virological or CD4 count outcomes, rather than as an outcome. Due to the highly effective modern ART regimens, treatment adherence is a key determinant of HIV treatment success[162;173;199;200;325].

2.2.2 **Identification of relevant studies**

The papers included in this review were identified by a systematic literature search of the electronic database PubMed in August 2016. Original research studies (of any design and including secondary observational analyses of Randomised Controlled Trial [RCT] data) were identified using the search terms shown in Figure 2.1 for the gender/sexual orientation review, and in Figure 2.2 for the SES review. Any literature reviews or Meta analyses identified by this search were also included in the review (although not included in the summary tables). Additional studies were identified by searching the websites of the following major observational studies:

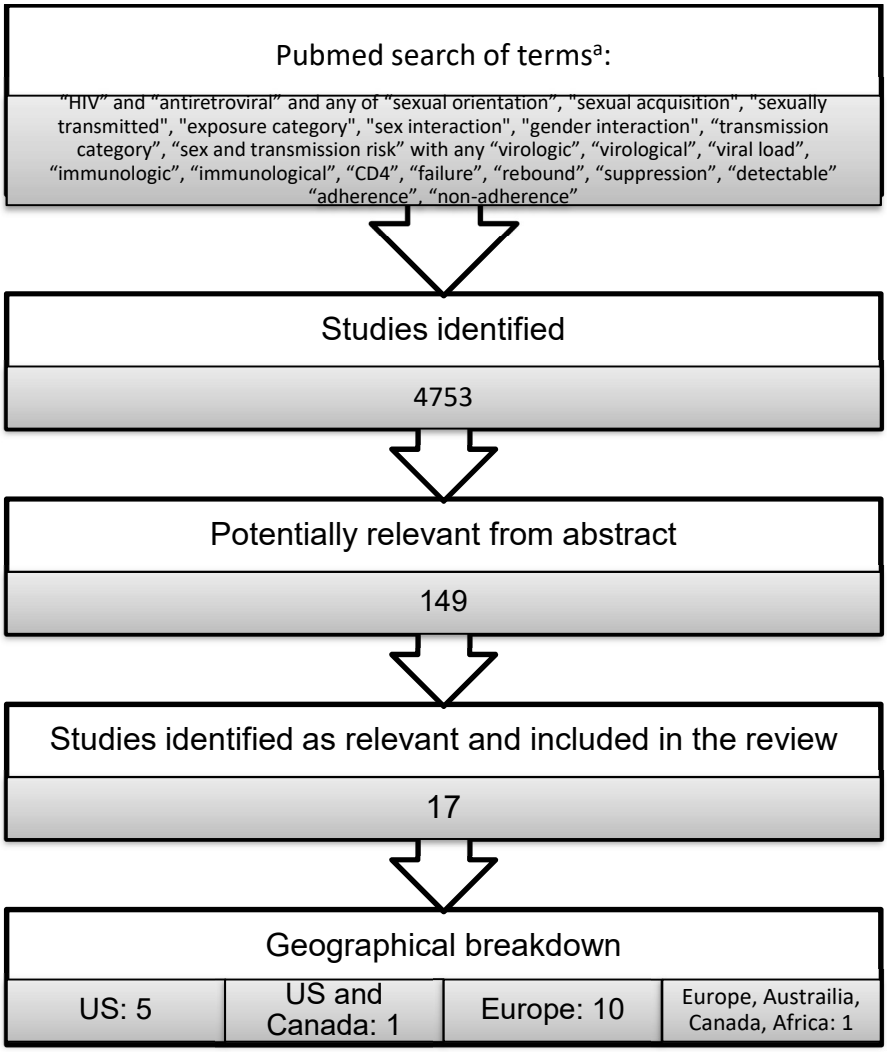
- AIDS Care Cohort to evaluate Exposure to Survival Services (ACCESS) study
- Agence Nationale se Recherches sur le Sida (ANRS) VESPA study
- ART Cohort Collaboration (ART-CC) study
- Antiretrovirals, Sexual Transmission Risk, and Attitudes (ASTRA) study
- AIDS Therapy Evaluation in the Netherlands (ATHENA) study
- Canadian Observational Cohort (CANOC) study
- Collaboration of Observational HIV Epidemiological Research Europe (COHERE) study
- Cohorte de la Red de Investigación en Sida (CoRIS)
- Danish HIV Cohort Study (DHCS)
- EuroSIDA

- HAART Observational Medical Evaluation and Research (HOMER) study
- Italian Cohort of Naïve Antiretrovirals (ICoNA) study
- North American AIDS Cohort Collaboration on Research and Design (NA-ACCORD) study
- Swiss HIV Cohort Study (SHCS)
- UK Collaborative HIV Cohort (CHIC) study.

The selection criteria for the literature reviews were as follows:

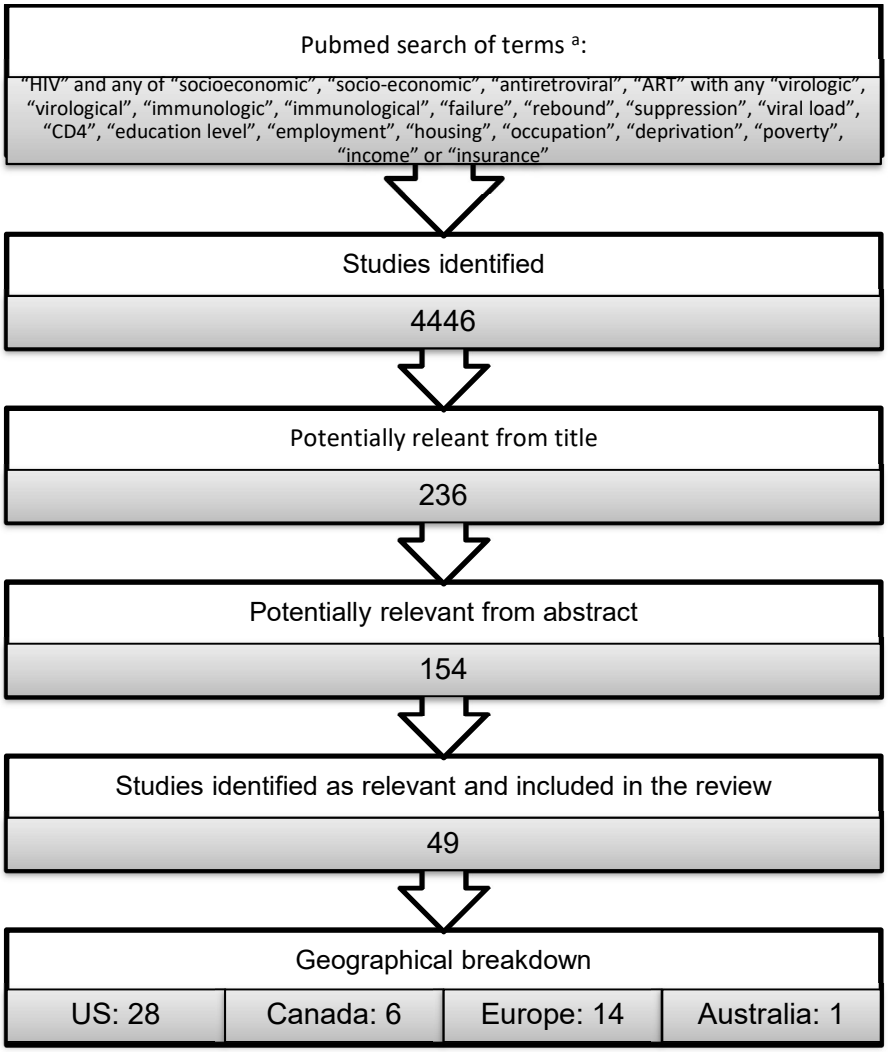
- Set in high-income counties
- Has individual-level data
- More than 100 participants
- At least some recruitment taking place from 2001 onwards (after the introduction of ritonavir (RTV)-boosted PIs)
- At least some participants prescribed ART
- Studies with virological and CD4 count outcomes that only report analyses adjusted for adherence were excluded since adherence is on the causal pathway between either gender/sexual orientation or SES and HIV treatment outcomes
- Written in English.

Figure 2.1: Flow diagram of literature search for studies investigating the association between gender/sexual orientation and virological ART response, CD4 count ART response and ART adherence



[a] Including MeSH terms.

Figure 2.2: Flow diagram of literature search for studies investigating the association between socio-economic factors and virological ART response, CD4 count ART response and ART adherence



[a] Including MeSH terms.

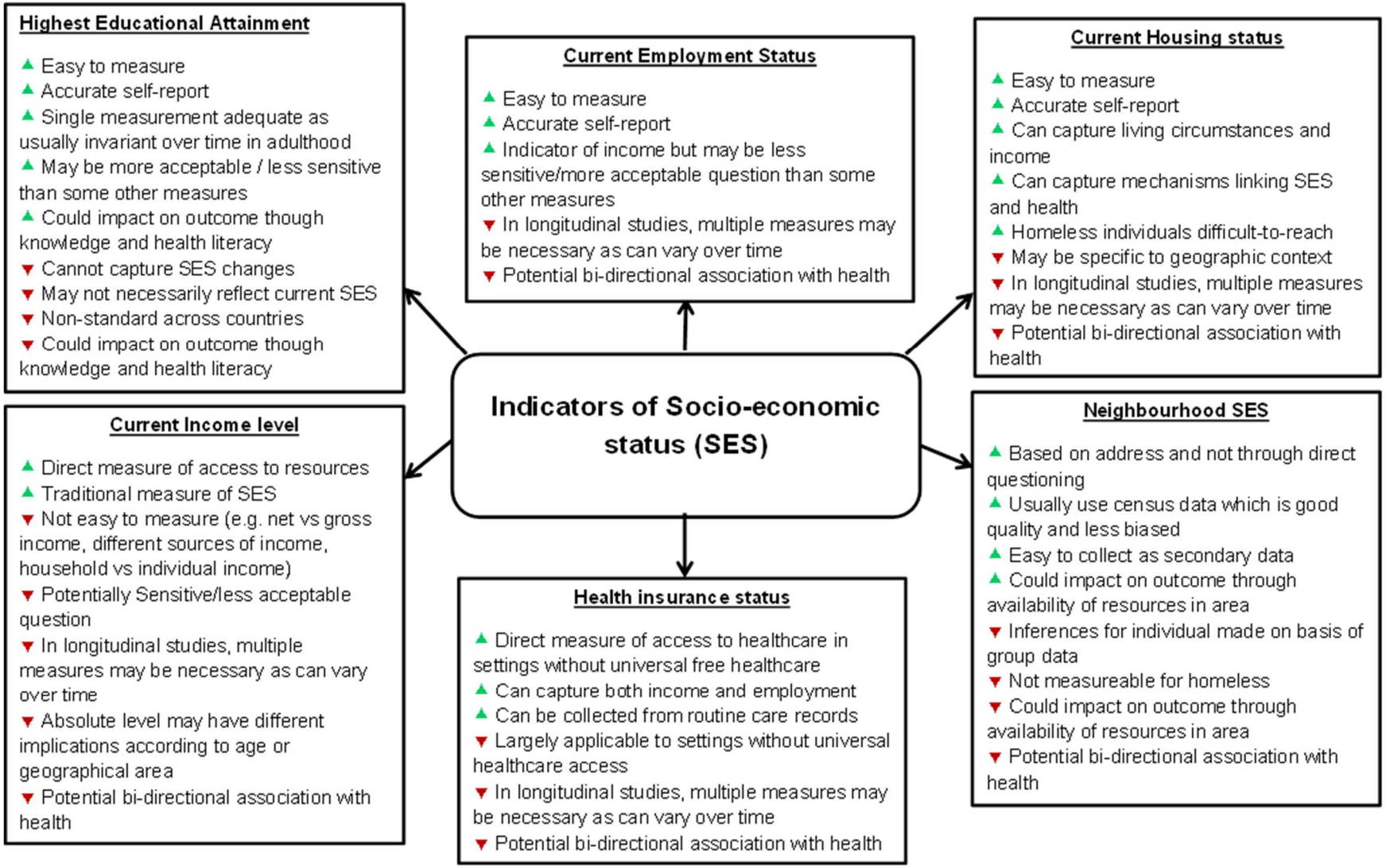
2.2.3 **Definition of gender, gender/sexual orientation and socio-economic factors**

For the gender-based section of my literature review, I considered any study which met the above selection criteria and which categorised individuals as men and women and did not divide these groups further by sexual orientation.

For the gender/sexual orientation-based systematic literature review, I considered any study which met the above selection criteria and which included MSM, MSW, and women as distinct groups, although not all three groups had to be included. Studies comparing heterosexual men and women were considered as part of this review rather than the gender-based review because MSM and MSM were still categorised as different groups in these studies, even though MSM were excluded. Although mode of HIV acquisition and sexual orientation are separate entities, I included studies that used either variable to categorise individuals. I also included studies that additionally divided women into two groups: women who have sex with men [WSM] and women who have sex with women [WSW].

In the SES-based systematic review, the following specific markers of SES were considered: education, employment, income/financial status, housing, health insurance and neighbourhood SES. The advantages and disadvantages of each of these factors as indicators of SES are set out in Figure 2.3 and discussed in the relevant subsections of this section[269;326;327].

Figure 2.3: Advantages and disadvantages of the indicators of SES



2.2.4 **Summary of the identified studies**

I summarised the results of the identified studies, according to whether they considered virological outcomes, CD4 count outcomes, or ART adherence outcomes. Studies were listed according to study design and then by number of participants. I presented the reported unadjusted and adjusted risk ratios (RR), odds ratios (OR), prevalence ratios (PR), and hazard ratios (HR) for the association between the explanatory variable (gender; gender/sexual orientation; or socio-economic factor) and the outcome of interest. I standardised all effect size estimates such that: for gender, men were the comparison group; for gender/sexual orientation, MSM were the comparison group, or MSW were the comparison group when comparing MSW and women; for SES, the lowest SES group was compared with the highest. In each review of the literature on ART adherence, the effect size estimates were standardised such that they were in terms of ART non-adherence rather than adherence. In the summary tables, all studies will be referred to only by their acronym (refer to list on pages 10-11).

2.3 **Review of the literature on gender and HIV treatment outcomes**

In this section, I summarised major studies that consider associations between gender (as a factor alone not combined with sexual orientation) and response to ART among people living with HIV (PLWH). These papers were identified during the systematic review of the literature for studies that considered the effect of gender/sexual orientation on HIV treatment outcomes, but could not be included since they did not split the men up into two groups. Since the studies were still of interest I have added a short summary of them here.

2.3.1 **Virological response to ART: Association with gender**

Numerous studies have considered gender as an explanatory variable, although not always as the primary factor of interest, when considering factors associated with virological response to HIV treatment. The observational studies reviewed are summarised in Table 2.1.

A meta-analysis of 40 clinical trials found no evidence of a difference in virological suppression at 48 weeks from ART initiation between men and women, however, particular trials included found that women had poorer virological outcomes[328]. People in trials may not be representative of the general HIV population, and so one may

expect a better response rate from individuals enrolled in trials and an underestimation of relative differences in treatment response.

A recent literature review of 65 observational studies considered gender disparities in mortality, progression to AIDS, virological and immunological response to ART[329], of which 68% found no statistically significant difference for any of the outcomes between men and women. In particular, they found pooled hazard ratios (women vs. men) of 0.93 (95% CI 0.85, 1.01) and 0.94 (0.89, 0.99) for virological failure and virological suppression, respectively.

Of 17 observational studies identified by my review, seven similarly found that women had a lower rate of virological suppression[92;330;331], and a greater risk of virological rebound[330;332-335] or virological failure[335]. In another study, the Royal Free HIV Cohort study (RFHCS), the setting of some of the analyses in this thesis, a comparable percentage of men and women experienced virological failure when those who discontinued ART were excluded from the analysis[336]. However, when treatment discontinuations were additionally considered as virological failure, 10% and 14% more women than men experienced virological failure at 48 and 96 weeks respectively.

Conversely, three other studies observed a better initial virological response to treatment in women than in men, including the Spanish GEEMA study[127] and two population-based studies of the HIV-positive population of New York[128;337]. The Spanish study, among treatment experienced individuals, found that men had a higher VL than women at all time-points following ART initiation[127]. Among these three studies, two were in study populations where individuals had not necessarily started ART, and one considered a population in which around 80% had experience of taking ARVs prior to ART initiation. Thus, these results may be reflecting differences in timing of ART initiation or in pre-ART differences. Furthermore, studies that found that men tended to have poorer outcomes had a greater proportion of women in the study population – 26-30% vs. 16-24% in studies finding women had poorer outcomes. Finally, the six remaining studies found no difference in time to VL <500copies/mL following ART initiation[335;338], virological suppression in the first 12 months of ART[339-341], and time to virological rebound[128;342] by gender. Thus, the literature considering differences in virological response to ART according to gender is very mixed.

Six studies adjusted for mode of HIV acquisition[333;335;337;338;340;341]. In four of these there were no gender differences after adjustment[335;338;340;341]; however, three of these did not present unadjusted results. In the other two studies, there was evidence that

gender differences were attenuated by adjustment for mode of HIV acquisition. In the ART Cohort Collaboration (ART-CC) study, the 58% higher rate of rebound among women in unadjusted analyses was attenuated to a 14% higher rate[333]. Additionally in a study of the New York HIV-positive population, though in unadjusted analyses women tended to have a lower prevalence of VL suppression than men, adjusting for mode of HIV acquisition and other baseline factors meant that women had 4% *greater* prevalence of VL suppression[337]. All of these studies adjusted for several factors simultaneously, so it was not possible to conclude whether gender differences were explained by differences in mode of HIV acquisition. Adjustment can also be problematic in this situation, as generally one of the mode of acquisition groups (commonly labelled as MSM, gay/bisexual or historically as homosexual) contains exclusively men.

Table 2.1: Original research studies considering the association between virological outcomes and gender among people prescribed ART [a]

Publication Setting, Study years and Study Group [b]	Study			Viral outcome definition (prevalence)	Estimate (95% CI) [c] Women vs Men			Factors adjusted for
	N	% Women	% MSM		Measure	Unadjusted	Adjusted	
Cross-sectional								
Torian 2014 AJPH[337] US, 2006-10 NYC HARS	87,146 HIV diagnosed	30%	36%	<400 (59%)	PR	0.99 (0.98, 1.00)	**1.04 (1.03, 1.06)**	HIV acquisition risk, age, ethnicity, country of birth, AIDS diagnosis
Longitudinal								
Vandenhende 2015 AIDS[333] Europe & N America 1996-2012 ART-CC	17,902 VL<50 in 3-9 mths of initiating ART	24%	42%	Two consecutive >500 (11%)	HR	**1.58 (1.39, 1.80)**	1.14 (0.97, 1.33)	HIV acquisition risk, age, 3rd ARV, yr ART start, VL & CD4 at ART start, CDC stage, low level viraemia
Robertson 2014 AIDS Care[128] US 2005-11 NYC HARS	12,318 HIV diagnosed	26%	42%	Time to <400 Subsequent time to >1000	HR	**1.17 (1.12, 1.23)** NS	**1.15 (1.10, 1.20)** NS	Age diagnosis, yr diagnosis, time to start ART, CD4 at diagnosis
Althoff, 2010, AIDS[338] US & Canada 1998-2008 NA-ACCORD	12,196 ART-naïve initiating ART with VL>500	17%	29%	Time until <500	OR	n/k	0.98 (0.92, 1.05)	HIV acquisition risk, age, ethnicity, initial ART regimen, yr of ART start, VL and CD4 at ART start, prior AIDS diagnosis, cohort
Smit, 2013, PLoS One[341] Netherlands 1996-2010 ATHENA	10,278 ART-naïve initiating ART[c]	16%	59%	<1,000 within 12 mths of ART initiation (95%)	HR	n/k	1.06 (0.98, 1.14)	HIV acquisition risk, age, region, time, VL & CD4 at ART start, ART regimen
Cescon, 2013, PLoS One[330] Canada 2000-11 CANOC	5,442 ART-naïve initiating ART	21%	n/k	2 consecutive <50 Subsequent>1000	HR	**0.72 (0.64,0.81)** **1.68 (1.34, 2.11)**	**0.82 (0.72, 0.93)** **1.31 (1.03, 1.66)**	Age, province, third ARV, VL & CD4 at ART start, yr of ART start, VL testing rate

Publication Setting, Study years and Study Group [b]	Study			Viral outcome definition (prevalence)	Estimate (95% CI) [c] Women vs Men			Factors adjusted for
	N	% Women	% MSM		Measure	Unadjusted	Adjusted	
Cescon, 2011, HIV Med[92] Canada 2000-08 CANOC	3,555 ART-naïve initiating ART, VL≥ 50	20%	n/k	Two consecutive <50	HR	**0.74 (0.68, 0.81)**	**0.86 (0.78, 0.94)**	Age, province, IDU, third ARV, VL and CD4 at ART start, prior AIDS diagnosis
Collazos, 2007, AIDS[127] Spain 1998-99 GEEMA	2,620 initiating NFV-based ART with VL>200	28%	14%	<200 at 12 mths after ART start	%	ARV experienced: **49% vs. 40%** ARV naïve: 79% vs. 74%	n/k	
Moore, 2003, JAIDS[335] Europe 1999-2001 EuroSIDA	2,548 PI and NNRTI naïve initiating ART	20%	48%	Time to <500 Time to two consecutive >500 Failure to reach <500 by wk 32	**HR**	0.93 (0.84, 1.03) **1.40 (1.18, 1.67)** **1.16 (1.03, 1.32)**	0.91 (0.81, 1.03) 1.17 (0.95, 1.44) 1.15 (0.98, 1.33)	HIV acquisition risk, age, ethnicity, geographical region, ART history, VL & CD4 at ART start, prior AIDS
Nicastri, 2005, AIDS[340] Italy 1996-99 IATG	2,460 PI and NNRTI naïve initiating PI-based ART, VL>500	28%	15%	<500 within 12 mths Two subsequent consecutive >500	HR	n/k	1.04 (0.92, 1.18) NS	HIV acquisition risk, age, VL & CD4 at ART start, prior AIDS
Saracino, 2016, Clin Microbiol Infect[342] Italy 2004-14 ICoNA	2,321 ART-naïve initiating ART ≥6 mths ago	21%	43%	Time to two consecutive >200 (3.3 per 100 pyrs)	RR	n/k	1.15 (0.71, 1.85)	Migrant status, employment status, first-line regimen type, CD4 at enrolment, CDC stage
Geretti, 2008, Antivir Ther[334] UK & Germany 1996-2005 Two centres	1,386 ART-naïve initiating ART, achieve VL≤ 50 & no VL>400 in 1st yr	21%	n/k	2 consecutive >400 or single >400 followed by ARV change/end of follow-up (26%)	IRR	**1.77 (1.11,2.82)**	**1.79 (1.12, 2.85)**	ART regimen and presence of low level viraemia in yr after virological suppression

Publication Setting, Study years and Study Group [b]	Study			Viral outcome definition (prevalence)	Estimate (95% CI) [c] Women vs Men			Factors adjusted for
	N	% Women	% MSM		Measure	Unadjusted	Adjusted	
Lima, 2010, J Acquir Immune Defic Syndr[332] Canada 2000-07 BC-CfE	1,305 ART-naïve initiating ART, achieve VL≤ 50	16%	n/k	2 consecutive >400 (21%)	% and OR	**37% vs. 18% p<0.01**	**1.68 (1.05, 2.69)**	Age, IDU, third ARV, nadir CD4, VL at ART start, yr of ART start, adherence, drug resistance, time suppressed [d]
Multhingham, 2013, JAIDS[339] US 2009-10 All HIV-positive residents of San Francisco	862 HIV diagnosed	7%	68%	<200 within 1 yr of diagnosis (50%) <200 within 1 yr of diagnosis among those retained in care (76%)	%	57% vs. 50% 81% vs. 76%	n/k	
Castillo, 2004, AIDS Care[331] Canada 1997-2002 BC-CfE	788 ART-naïve initiating ART	18%	n/k	Time to 2 consecutive <500	HR	**0.69 (0.55, 0.86)**	0.80 (0.63, 1.01)	Age, IDU, VL & CD4 at ART start, physician experience, pharmacy dispensing site
Pence, 2008, JAIDS[343] US 2001-02 CHASE	474 on ART, VL<400 at enrolment	30%	n/k	Time to ≥400	HR	n/k	0.92 (0.49, 1.74)	Age, ethnicity, insurance, 1st line ART, time on regimen, alcohol, depression, drug use, trauma, recent stress, social support, self-efficacy
Smith, 2007, JAIDS[336] UK 1996-2006 RFHCS	433 ART-naïve initiating EFV-based ART	22%	55%	OT: 2 consecutive >500 by wk 48 OT: 2 consecutive >500 by wk 96 ITT: 2 consecutive >500 by wk 48	% (95% CI)	1.3% (0.0, 3.9) vs 3.8% (1.6, 6.0) 4.4% (0.0,9.3) vs 5.8% (3.0,8.6) **39% (29, 49) vs 29% (24, 34)**	n/k	

Publication Setting, Study years and Study Group [b]	Study			Viral outcome definition (prevalence)	Estimate (95% CI) [c] Women vs Men			Factors adjusted for
	N	% Women	% MSM		Measure	Unadjusted	Adjusted	
				ITT: 2 consecutive >500 by wk 96		**57% (46, 68) vs 43% (38, 49)**		

Red= VL outcomes of men were better than those of women; Green= VL outcomes of women were better than that of men; **bold**= estimates with an associated P-value<0.05.

[a] Studies ordered by study size within each category (cross-sectional and longitudinal); [b] refer to list of relevant study acronyms on pages 10-11 for full study names; [c] estimates are standardised such that men are the reference group; [d] adjusted for adherence which is on the causal pathway; n/k=not known; NS= non-significant association but no specific estimates given; yr=year; mth=month; wk=week; pyrs=person years; PI=Protease Inhibitor; NNRTI=Non-Nucleoside Reverse Transcriptase Inhibitor; EFV=efavirenz; OT=on treatment analysis; ITT=intent-to-treat analysis; CD4=CD4 cell count; IDU=injection drug use; HCV=hepatitis C virus; CI=Confidence Interval; OR=Odds Ratio; PR=Prevalence Ratio; HR=Hazard Ratio; RR=Risk Ratio; IRR= Incidence Rate Ratio.

2.3.2 **Immunological response to ART**

I identified fewer studies (seven) comparing immunological response to ART (as measured by changes in the CD4 count) between genders (Table 2.2). One study was conducted in the USA, and six were conducted in Western Europe. A global review identified four observational studies with a pooled risk ratio for immunological failure of 0.83 for women compared to men[329]. Four of the seven studies found improved immunological outcomes for women[127;338;341;344]. In contrast, only one reported any evidence of improved CD4 count response among men compared to women at 12 weeks after ART initiation, and this difference was not statistically significant (p=0.24) and did not persist in the longer-term[336]. This study had the highest proportion of men reporting sex between men as the likely route of HIV acquisition (71%). The two remaining studies found no evidence of differences in immunological response between men and women, however, these contained the smallest number of participants and so they may have had less power to detect gender differences[335;340].

Table 2.2: Original research studies considering the association between CD4 outcomes and gender among people prescribed ART [a]

Publication Setting, date and study [b]	Study characteristics			CD4 count outcome definition	Estimate (95% CI) [c d] Women vs Men			Factors adjusted for
	n	% Women	% MSM		Measure	Unadjusted	Adjusted	
Althoff, 2010, AIDS[338] US and Canada 1998-2008 NA-ACCORD	12,196 ART-naïve initiating ART with VL>500	17%	n/k	Time to 100 increase	HR	n/k	**1.13 (1.05, 1.21)**	HIV acquisition risk, age, ethnicity, initial ART regimen, yr ART of start, VL and CD4 at ART start, prior AIDS diagnosis, cohort
Smit, 2013, PLoS One[341] Netherlands 1996-2010 ATHENA	10,278 ART-naïve initiating ART [d]	16%	59%	Increase by 150 in first yr (70%)	HR	n/k	**1.26 (1.14, 1.38)**	Mode of HIV acquisition, age, region, time, VL and CD4 at ART start, ART regimen
Kesselring, 2010, Antivir Ther[344] Netherlands 1996-2009 ATHENA	6,057 ART-naïve initiating ART with VL <400 by 9 mths, exclude if 2 VL≥400 or >30d not on ART	19%	56%	Change 0 to 6 mths Change 6 mths to 3 yrs	Mean difference	**+26, p<.0001** **+35, p<.0001**	n/k	
Collazos, 2007, AIDS[127] Spain 1998-99 GEEMA	2,620 initiating nelfinavir regimen with VL>200	28%	14%	Change at 1 yr	Median	ARV experienced: +91 vs. +81, p=0.1 ARV naïve: **+212 vs. +147 p=0.002**	n/k	
Moore, 2003, JAIDS[335] Europe 1999-2001 EuroSIDA	2,548 PI and NNRTI naïve initiating ART	20%	48%	Time to 100 increase	HR	0.96 (0.86, 1.70)	1.02 (0.88, 1.14)	HIV acquisition risk, age, ethnicity, geographical region, treatment history, VL and CD4 at ART start, prior AIDS diagnosis

Publication Setting, date and study [b]	Study characteristics			CD4 count outcome definition	Estimate (95% CI) [c d] Women vs Men			Factors adjusted for
	n	% Women	% MSM		Measure	Unadjusted	Adjusted	
Nicastri, 2005, AIDS[340] Italy 1996-99 IATG	2,460 PI and NNRTI naïve initiated PI-based ART with VL>500	28%	15%	1 yr 2 yrs 3 yrs 4 yrs	Median (IQR)	336 (219-528) vs. 313 (181-488) 414 (252-590) vs. 375 (226-569) 437 (282-630) vs. 407 (250-613) 465 (277-632) vs. 430 (267-651)	n/k	
Smith, 2007, JAIDS[336] UK 1996-2006 RFHCS	433 ART-naïve initiated EFV containing regimen	22%	55%	Change at 12 wks Change at 48 wks Change at 120 wks	Median (IQR)	+87 (+44, +54) vs. +104 (+53, +173), p=0.24 +166 (+89, +239) vs. +176 (+93, +263) +303 (+171, +414) vs. +249 (+124, +375), p=0.33	n/k	

Red= CD4 count outcomes of men were better than those of women; Green= CD4 count outcomes of women were better than that of men; **bold**= estimates with an associated P-value<0.05.

[a] Studies ordered by study size within each category (cross-sectional and longitudinal); [b] refer to list of relevant study acronyms on pages 10-11 for full study names; [c] estimates are standardised such that men are the reference group; [d] CD4 count estimates in cells/μL; n/k=not known; yrs=years; mths=months; wks=weeks; PI=Protease Inhibitor; NNRTI=Non-Nucleoside Reverse Transcriptase Inhibitor; EFV=efavirenz; CD4=CD4 cell count; CI=Confidence Interval; HR=Hazard Ratio; IQR=Interquartile Range.

2.3.3 **ART non-adherence**

In a previous literature review of 44 observational studies, in high-income or upper-middle income countries, published between 2000 and 2011, 30 found poorer adherence to ART among women than men, though only nine of these reached statistical significance[345]. Only one found lower adherence among men compared to women. The authors noted that all studies which used a cut-off of 100% or ≥95% adherence as constituting "good" adherence found women had a lower mean adherence than men, but studies using cut offs of ≥90% or ≥80% found that women had a higher mean adherence.

A summary of studies of the association between gender and ART adherence are displayed in Table 2.3. Five cross-sectional observational studies were considered (one from Switzerland and four from USA/Canada). All studied individuals on ART, regardless of length of exposure, and had a self-reported adherence outcome. All found that women had higher odds of self-reported ART non-adherence compared to men, with adjusted odds ratios varying from 1.14 to 1.68[346-350].

There were also five longitudinal observational studies, with far more mixed findings than the cross-sectional studies. Three, from the USA, had objective endpoints of prescription refill[351] and MEMS[352;353] and each found lower adherence in women than in men. One Spanish study[127] considered self-reported adherence and found no evidence of differences between genders. The population studied in this case included the highest number of IDU and lower number of MSM of any of the studies considered. Finally, a large study of over 6000 participants from the SHCS considered changes in adherence[354]. Women had 10% greater odds of worsening adherence and 16% greater odds of improving adherence compared to men in adjusted analyses. This study was inconclusive about the effect of gender on changes in adherence. However, this was not the focus of the study, so unadjusted results were not reported and the adjusted model included a large number of variables.

Table 2.3: Original research studies considering the association between adherence to ART and gender among people prescribed ART [a]

Publication Setting, date and study [b]	Study			Non-adherence outcome definition		OR (95% CI) Women vs Men [c d]		Factors adjusted for
	n	% Women	% MSM	Self-report	Definition (prevalence)	Unadjusted	Adjusted	
Cross-sectional								
Glass, 2006, JAIDS[346] Switzerland 2003 SHCS	3,607 on ART ≥6 mths	29%	n/k	Yes	Missed ≥1 dose last 4 wks (31%) Missed ≥2 doses last 4 wks (15%) <95% last 4 wks (7%)	**1.20 (1.03, 1.41)** **1.23 (1.01, 1.49)** 1.28 (0.98, 1.69)	1.14 (0.95, 1.45) 1.11 (0.88, 1.39) 1.02 (0.74, 1.39)	Age, ethnicity, living alone, education, time on ART, current IDU, psychiatric treatment, lipodystrophy, number previous regimens, dose frequency, current regimen
Beer, 2012, Open AIDS J[347] US 2007-08 MMP	3,307 on ART	25%	n/k	Yes	<100% dose last 48 hrs (13%) <100% schedule last 48 hrs (27%) <100% instruction last 48 hrs (30%)	**1.55 (1.24, 1.92)** **1.66 (1.40, 1.97)** NS	**1.36 (1.07, 1.74)** **1.46 (1.20, 1.76)** NS	Age, ethnicity, education, public assistance, depression, crack use, homelessness, amphetamine use, binge drinking, time on ART, dose frequency, time since diagnosis, knew VL, resistance discussed
Raboud, 2011, AIDS Behav[348] Canada 2007-09 OCS	779 on ART	15%	69%	Yes	<100% last 4 dys (15%)	1.45 (0.88, 2.44)	N/A	N/A
O'Neil, 2012, J Int Assoc Physicians AIDS Care[349] Canada 2007-10 LISA	556 on ART	27%	n/k	No	Prescription refill <95% 1 yr (44%)	n/k	**1.68 (1.07, 2.64)**	Age, ethnicity, education, income, housing stability, IDU, history of incarceration, depressive symptoms, illicit drug use, methadone treatment, ART frequency, medication, memory aids, in assisted therapy program

Publication Setting, date and study [b]	Study			Non-adherence outcome definition		OR (95% CI) Women vs Men [c d]		Factors adjusted for
	n	% Women	% MSM	Self-report	Definition (prevalence)	Unadjusted	Adjusted	
Kyser, 2011, AIDS Care[350] US 2004-06 SUN	528 on ART	22%	56%	Yes	<100% last 3 dys (16%)	**1.68 (1.00, 2.82)**	1.21 (0.53, 2.79)	Ethnicity, education, employment, time since HIV diagnosis, suicidal ideation, mental and physical health scores, alcohol use, marijuana use, cocaine use, tobacco use, exercise
Longitudinal								
Glass, 2010, JAIDS[354] Switzerland 2003-09 SHCS	6,709 on ART	30%	38%	Yes	100% to <100% last 4 wks 2 measurements 6 mths apart (17%) <100% to 100% last 4 wks 2 measurements 6 mths apart (18%)	n/k	1.10 (0.98, 1.23) 1.16 (0.97, 1.39)	Age, ethnicity, education, living alone, stable partnership, IDU, drug maintenance program, alcohol, smoking, started riskier sex, psychiatric treatment, released from prison, hospitalised, co-medication, time living with HIV, change in ART, regimen frequency, time on ART, lipodystrophy, change in physician, adherence at first visit
Silverberg, 2009, J Gen Intern Med[351] US 1996-2005 KPNC	4,686 initiating ART	10 %	64%	No	Prescription refill difference in mean over 2 yrs since ART initiation	n/k	**-4.2% (-7.2%, -1.2%), p=0.006**	Mode of HIV acquisition, age, ethnicity, insurance, neighbourhood SES, yr ART initiation, VL and CD4 at ART start, ART experience, ART regimen, HCV, depression, comorbidities
Collazos, 2007, AIDS[127] Spain 1998-99 GEEMA	2,620 initiating NFV-based ART with VL>200	28%	14%	Yes	<100% last 3 mths (at 3, 6, 9 mths after ART initiation)	n/k but no association (p=0.1 to p=0.9)	n/k	

Publication Setting, date and study [b]	Study			Non-adherence outcome definition		OR (95% CI) Women vs Men [c d]		Factors adjusted for
	n	% Women	% MSM	Self-report	Definition (prevalence)	Unadjusted	Adjusted	
Simoni, 2012, JAIDS[353] US 1997-2009 MACH14	1,809 on ART	33%	n/k	No	MEMS mean over 4-wk periods	65% vs. 69%	0.96 (0.83, 1.11)	Age, ethnicity, site, education, income, substance use, depression
Berg, 2004, J Gen Intern Med[352] US 1998-2001 HERO	113 current/ former opioid users	43%	n/k	No	MEMS median across study period	**46% (18%-77%) vs 73% (30%-93%), p=0.04**	n/k	

Red= adherence outcomes of men were better than those of women; Green= adherence outcomes of women were better than that of men**; bold**= estimates with an associated P-value<0.05.

[a] Studies ordered by study size within each category (cross-sectional and longitudinal); [b] refer to list of relevant study acronyms on pages 10-11 for full study names; [c] estimates are standardised such that men are the reference group; [d] standardised such that non-adherence is the outcome; OR=Odds Ratio; CI=Confidence Interval; n/k=not known; NS= non-significant association but no specific estimates given; N/A=not applicable; yr/s=year/s; mths=months; wks=weeks; dys=days; hrs=hours; NFV=nelfinavir; MEMS=Medical Event Monitoring System; CD4=CD4 cell count; IDU=injection drug use; HCV=hepatitis C virus.

2.4 **Review of the literature on gender/sexual orientation and HIV treatment outcomes**

This section of my literature review evaluated studies that have considered the association of HIV treatment outcomes with gender/sexual orientation, as a combined variable.

2.4.1 **Virological response to ART**

Fifteen studies considered the association between gender/sexual orientation and virological response to ART[126;355-368], of which four were cross-sectional and 11 longitudinal. The results of these studies are summarised in Table 2.4.

2.4.1.1 ***MSW vs MSM***

When focusing on the comparison between the two male groups, eight of nine studies which considered the outcome of virological suppression found that MSW had a lower prevalence[355;356], lower adjusted odds (aOR varying between 0.54 to 0.80[357-359]), or lower adjusted rate (aHR=0.83-0.91[360-362]) of virological suppression compared to MSM. The US-based HIV Outpatient Study (HOPS) did not find a difference in time to virological suppression between MSW and MSM despite a higher prevalence of late diagnosis among MSW[363]. There are a number of potential explanations for the difference of the HOPS results to the rest of the literature. Since only individuals who were linked to care and enrolled in the HOPS within six months of diagnosis were included, it may have resulted in the inclusion of individuals with more favourable virological outcomes. HOPS was the study with the fewest number of participants (N=926), although the differences were not so imprecise that this could explain the difference. In contrast to the other studies, HOPS adjusted for insurance status and private vs. public clinic, thus it is possible that these differences could have explained the differences between MSW and MSM in this study.

Of four studies which considered virological non-suppression/failure, three found poorer virological response to ART among MSW compared to MSM[362;364;365]. Two of these were in the RFHCS, the setting of some chapters in this thesis and one in the French Agence Nationale se Recherches sur le Sida (ANRS) study. On the other hand, in the Collaboration of Observational HIV Epidemiological Research Europe (CASCADE) study, there was no evidence of a difference in the rate of initial virological non-suppression/ rebound[366]. This study included a particularly high proportion of MSM compared to the other studies (74%) and a small proportion of MSW (11%), and was a seroconverters cohort. In addition, the study population included individuals in low-income countries (sub-Saharan Africa) as well as high-

income countries, and associations of gender/sexual orientation may not have been generalisable between high- and low-income countries.

In the SHCS, latent class analysis was used to allocate individuals into seven groups by highest membership probability[357]. Older MSW and single heterosexual migrants had aORs of 0.54 and 0.58 for VL suppression after six months of ART compared to MSM, respectively. However, when those who acquired HIV through heterosexual sex were considered as a single group, they had a more attenuated aOR of 0.72 compared to MSM. The results of this study provide some support for analysing groups with demographic factors in mind rather than solely by mode of HIV acquisition.

2.4.1.2 ***Women vs MSM***

Of eight studies which considered initial virological suppression as an outcome, five found evidence of a lower prevalence[355;356], odds[358;359], or rate[361] among women compared to MSM. These studies took place in both US-based[355;356] and European[358;359;361] observational cohorts. On the other hand, in the North American AIDS Cohort Collaboration on Research and Design (NA-ACCORD)[360] study, the RFHCS[362], and HOPS[363] there was no evidence of a difference. Previous studies have observed more frequent VL monitoring among men[330;369;370] or MSM[371] compared to women or heterosexuals, respectively; therefore, since all three studies used time-to-event analyses, the results are potentially subject to bias. Additionally, two of these studies restricted participation to individuals who had a timely ART initiation/linkage to care[360;363] which may have resulted in selection bias, and hence accounted for any differences.

Two of three studies considering endpoints of virological failure found women had poorer outcomes compared to MSM: in the RFHCS[362] (aHR=3.3 and 4.7) and the ANRS study (aOR=6.9 among migrant women vs. MSM)[364]. Similarly to the comparison between MSW and MSM, the CASCADE study did not find any evidence of a difference between initial virological non-suppression/rebound in women and MSM[366].

2.4.1.3 ***Women vs MSW***

All six studies comparing virological suppression outcomes between women and MSW found little evidence of a difference between women and MSW. In three studies there was no difference in the odds or prevalence of virological suppression[355;361;368] and, though in two further studies there were differences in unadjusted analyses (in opposite directions), these were attenuated by adjustment for baseline factors[126;367]. The remaining study from the RFHCS showed weak evidence of a higher rate of virological suppression among women[362].

Two UK-based studies additionally considered an outcome of virological failure/rebound and found some evidence of a greater rate of VL failure among women compared to MSW[362;367]. Adjustment for baseline factors (including demographics, VL and CD4 count at ART initiation) substantially attenuated any associations. However, when pregnant women were excluded from the UK CHIC study, men had a 33% higher rate of virological rebound than the remaining women[367]. This and other studies have shown that part of the reason for a higher prevalence of rebounds among women are the greater ART discontinuations among postpartum women and poorer ART adherence in pregnancy[372].

Table 2.4: Original research studies considering the association between virological outcomes and gender/sexual orientation among people prescribed ART [a b]

Publication Setting, date and study [c]	Study characteristics	Viral outcome definition (prevalence)	Prevalence of gender/sexual orientation groups		Main results: Estimate (95% CI) [d]			Factors adjusted for
			Group	%	Measure	Unadjusted	Adjusted	
Cross-sectional								
Hall 2013, JAMA Intern Med[355] US 2009 MMP and NHSS	378906 prescribed ART in US in 2009	Most recent <200 (78%)	MSM MSW WSM PWID	52% 9% 18% 16%	%	**82%** **74%** **74%** -	n/k	
Cohen 2014, JAIDS[356] US 2010 NHSS	42363 ≥1 CD4 or VL in 2010 with any further tests <3 mths apart	Most recent <200 (48% of engaged in care; 74% of retained in continuous care)	MSM MSW WSM PWID Other	51% 7% 17% 23% 2%	PR	1.00 **0.94 (0.93, 0.95)** **0.92 (0.91, 0.92)** - -	n/k	
D'Almeida, 2016, Antivir Ther[359] France 2011-12 ANRS-VESPA2	1246 on ART ≥12 mths	<50 for at least 6 mths (78%)	MSM non-African MSW non-African WSM MSW from SSA WSM from SSA PWID	35% 15% 11% 12% 24% 3%	OR	1.00 1.0 (0.6, 1.5) 0.8 (0.4, 1.4) **0.5 (0.3, 0.9)** 0.7 (0.5, 1.1) -	1.00 1.2 (0.6, 2.1) 1.7 (0.9, 3.4) 0.8 (0.4, 1.7) 1.0 (0.5, 2.0) -	Employment status, material deprivation, education, health literacy, social network, late ART initiation, HIV-related discrimination, ART adherence [e]
Dray-Spira 2007, AIDS[364] France 2002-03 ANRS-VESPA	896 on ART ≥6 mths	Detectable and CD4<200 (3.4%)	MSM French MSW French WSM migrant MSW migrant WSM PWID	38% 17% 10% 11% 11% 12%	% and OR	1.4% 4.1% 0.9% 6.7% 4.1% -	1.00 2.75 (0.68, 11.1) 0.63 (0.07, 6.09) **8.23 (1.77, 38.3)** **6.91 (1.03, 46.3)** -	Age, pre 1996 diagnosis, time on ART, AIDS at ART start, HCV, VL & CD4 at ART start, depressive symptoms, current drug use, HIV care interruption, ART adherence [e]
Longitudinal								
Hanna 2013, CID[360] US and Canada 2001-09 NA-ACCORD	5329 ART-naïve, initiating ART within 6 mths of eligibility	Time to <500 within 12 mths of ART start (55% in 2001, 81% in 2009)	MSM MSW Women PWID	43% 20% 22% 15%	HR	n/k	1.00 **0.91 (0.84, 0.99)** 0.99 (0.91, 1.08) -	Age at eligibility, ethnicity, eligibility criteria, psychosocial barriers, yr eligibility, province residence, VL at eligibility

Publication Setting, date and study [c]	Study characteristics	Viral outcome definition (prevalence)	Prevalence of gender/sexual orientation groups		Main results: Estimate (95% CI) [d]			Factors adjusted for
			Group	%	Measure	Unadjusted	Adjusted	
Zugna 2012, Antivir Ther[366] Canada, Australia, Europe, Africa 2011 CASCADE	4337 ART-naïve, on ART ≥90 dys	>500 six mths after ART start or <500 at 6 mths followed by two >1000 (10%)	MSM MSW Women Other	74% 11% 13% 1%	HR	n/k	1.00 0.91 (0.65, 1.27) 1.07 (0.80, 1.43) -	Age, ART regimen, VL and CD4 at ART start, started ART within yr of seroconversion, yr ART start
Rosin, 2014, HIV Med[126] Switzerland 1998-2011 SHCS	3,925 ART-naïve initiating ART	<50 at 1 yr (77%)	MSW Women	50% 50%	OR	1.00 **0.83 (0.72, 0.96)**	1.00 0.87 (0.73, 1.04)	Age, ethnicity, IDU, education, time, VL and CD4 at ART start, previous AIDS, HCV
Barber, 2011, Antivir Ther[367] UK 1998-2007 UK CHIC	3,666 ART-naïve initiating ART	Time to <50 Time to two subsequent >500 <50 at 6 mths <50 at 12 mths	MSW Women MSW Women MSW Women MSW Women	41% 59%	HR HR OR OR	1.00 **1.12 (1.04, 1.22)** 1.00 **1.30 (1.08, 1.59)** 1.00 0.95 (0.81, 1.12) 1.00 **0.81 (0.68, 0.96)**	1.00 1.06 (0.97, 1.16) 1.00 0.85 (0.68, 1.08) 1.00 1.09 (0.88, 1.32) 1.00 0.94 (0.76, 1.18)	Age, ethnicity, ART regimen type, yr ART start, VL and CD4 at ART start, previous AIDS diagnosis
Costagliola, 2012, Lancet Infect Dis[358] Europe 2000-09 COHERE	2,476 started ART, previously had TCVF [f]	<50 after TCVF [e] (17% in 2000, 49% in 2008)	MSM MSW Women PWID	28% 21% 26% 14%	OR	1.00 **0.77 (0.66, 0.91)** **0.67 (0.57, 0.78)** -	1.00 **0.77 (0.64, 0.93)** **0.63 (0.52, 0.75)** -	Age, VL and CD4 at TCVF [f], AIDS diagnosis, previous VL<50, drug failures before TCVF [f]

Publication Setting, date and study [c]	Study characteristics	Viral outcome definition (prevalence)	Prevalence of gender/sexual orientation groups		Main results: Estimate (95% CI) [d]			Factors adjusted for
			Group	%	Measure	Unadjusted	Adjusted	
Fardet 2006, HIV Med[361] France 1997-2001 ANRS	2,225 prescribed ART, started ART with VL>500	Time to <500	MSM MSW WSM PWID Other WSM MSW	32% 20% 26% 10% 12%	HR	n/k	1.00 **0.86 (0.73, 0.98)** **0.89 (0.75, 0.98)** - - 1.00 1.04 (0.89, 1.21)	Age, ART type, VL and CD4 at ART start, period of ART start
Lampe 2007, Arch Intern Med[365] UK 1999-2004 RFHCS	1,698 On ART	>50 in yr (36.9% in 1999- 14.5% in 2004) >50 received ART for ≥24 wks (31.2% in 1999 – 10.1% in 2004)	MSM White MSW White women Non-white MSW Non-white women MSM White MSW White women Non-white MSW Non-white women	63% 4% 5% 10% 17% 4% 5% 10% 17%	RR	n/k	1.00 n/k n/k **1.35 (1.15, 1.59)** n/k 1.00 n/k n/k **1.42 (1.14, 1.82)** n/k	Age, calendar period, time since first clinic visit
Keiser 2013, AIDS Behav[357] Switzerland 2000-08 SHCS	1,180 ART-naïve initiating ART, ≥6 mths follow-up	<50 6 mths after ART initiation (75.3%)	older MSM young MSM MSW and WSM Older MSW PWID Single migrants Migrant women in partnership MSM (all) Heterosexual (all)	35% 4% 20% 10% 13% 10% 9% **0.70 (0.52, 0.94)**	OR	1.00 2.11 (0.73, 6.12) 0.79 (0.55, 1.15) 0.69 (0.44, 1.08) - **0.50 (0.31, 0.82)** 0.82 (0.50, 1.35) 1.00	1.00 2.52 (0.84, 7.56) 0.80 (0.54, 1.18) **0.54 (0.32, 0.93)** - **0.58 (0.34, 0.99)** 0.97 (0.56, 1.66) 1.00 0.72 (0.50, 1.03)	Age, ART type, VL and CD4 at ART start, HIV stage Additionally adjusted for gender

Publication Setting, date and study [c]	Study characteristics	Viral outcome definition (prevalence)	Prevalence of gender/sexual orientation groups		Main results: Estimate (95% CI) [d]			Factors adjusted for
			Group	%	Measure	Unadjusted	Adjusted	
Saunders 2015, HIV Med[362] UK 2006-12 RFHCS	1,086 ART-naïve initiating ART	Time to <50	MSM MSW Women	52% 19% 29%	HR	1.00 0.91 (0.77, 1.08) 1.04 (0.91, 1.20)	1.00 0.83 (0.67, 1.03) 0.95 (0.78, 1.17)	Age, ethnicity, ART backbone, pre-ART VL and CD4, yr starting ART, time from diagnosis to ART start
			MSW Women			1.00 1.14 (0.95, 1.37)	1.00 1.15 (0.93, 1.41)	
		Time to two consecutive >200 after >6 mths ART (censored at discontinuation)	MSM MSW Women			1.00 **2.03 (1.12, 3.69)** **3.13 (1.92, 5.10)**	1.00 **3.64 (1.69, 7.83)** **4.74 (2.29, 9.84)**	
			MSW Women			1.00 1.54 (0.88, 2.70)	1.00 1.30 (0.70, 2.44)	
		Time to two consecutive >200 after >6 mths ART	MSM MSW Women			1.00 1.58 (0.99, 2.52) **2.98 (2.09, 4.25)**	1.00 **2.32 (1.28, 4.22)** **3.28 (1.91, 5.64**)	
			MSW Women			1.00 **1.89 (1.20, 2.94)**	1.00 1.41 (0.86, 2.33)	
Novak 2015, JAIDS[363] US 2000-13 HOPS	926 ART-naïve initiating ART	Time to first <500	MSM MSW Women Other	53% 17% 23% 8%	HR	1.00 0.9 (0.7, 1.1) **0.8 (0.7, 1.0)** -	1.00 1.1 (0.8, 1.3) 1.0 (0.8, 1.2) -	Age, ethnicity, IDU, insurance, private or public clinic, date diagnosis, VL and CD4 at ART start
Thorsteinsson, 2012, BMC Infect Dis[368] Denmark 1997-2009 DHCS	908 initiating ART	<500 at 1 yr	MSW Women	48% 52%	% and OR	92% 83%	1.00 0.81 (0.47, 1.39)	Age, ethnicity, period of ART initiation, previous AIDS diagnosis
		<500 at 3 yrs	MSW Women			87% 82%	1.00 1.09 (0.62, 1.89)	
		<500 at 6 yrs	MSW			87%	1.00	

Publication Setting, date and study [c]	Study characteristics	Viral outcome definition (prevalence)	Prevalence of gender/sexual orientation groups		Main results: Estimate (95% CI) [d]			Factors adjusted for
			Group	**%**	**Measure**	**Unadjusted**	**Adjusted**	
			Women			83%	1.15 (0.54, 2.44)	

Blue= MSM had improved virological outcomes than other gender/sexual orientation group; Red= MSW had improved virological outcomes than other gender/sexual orientation group; Green= Women had improved virological outcomes than other gender/sexual orientation group; **bold**= estimates with an associated P-value<0.05.

[a] Studies recruited not entirely before 2001, with sample size >100; [b] studies ordered by study size within each category (cross-sectional and longitudinal); [c] refer to list of relevant study acronyms on pages 10-11 for full study names; [d] estimates are standardised such that the MSM is the reference group; [e] adjusted for adherence which is on the causal pathway; [f] TCVF=Triple class virological failure: VL>500 despite ≥4 months continuous ART use to at least 1 PI, 1 NNRTI and 2 NRTI; MSM= men who have sex with men; MSW= men who have sex with women; WSM= women who have sex with men; PWID= people who inject drugs; n/k=not known; yr/s=year/s; mths=months; wks=weeks; IDU= injection drug use; HCV=hepatitis C virus; CI=Confidence Interval; PR=Prevalence Ratio; OR=Odds Ratio; HR=Hazard Ratio; RR=Risk Ratio.

2.4.2 **Immunological response to ART**

My literature review identified seven studies investigating the association between gender/sexual orientation and CD4 count response to ART[126;361;362;364;365;367;368]. All seven were longitudinal studies that took place in European settings (Table 2.5).

2.4.2.1 ***MSW vs MSM***

There was evidence of a poorer CD4 count response to ART among MSW compared to MSM in three of four studies which included MSM[361;364;365], whereas the remaining study found this in the shorter term but not the longer-term[362]. In a cross-sectional UK study, black African MSW had 2.4 times the adjusted risk of a CD4 count <200 cells/μL compared to MSM among individuals in care[365]. Though the proportion of white MSW with low CD4 count was consistently above that of MSM, there was no direct comparison of MSM and white MSW made. The results of another UK-based study found differences between MSM and MSW at 12 months but not at 24 months[362], potentially reflecting the lower pre-ART CD4 counts among MSW.

2.4.2.2 ***Women vs MSM***

All three studies comparing the CD4 count response on ART of women and MSM found that women had poorer outcomes[361;362;364]. Dray-Spira et al. found that migrant women had over twice the odds of failure to increase CD4 count by 100 cells/μL compared to MSM, even after adjustment for adherence to ART[364]. However, the outcomes of non-migrant women and MSM were similar. In another French study, similarly, there was evidence that heterosexual women took longer to see an increase in CD4 count of 100 cells/μL[361]. In a UK-based study, women had smaller median changes in CD4 count one and two years after ART initiation compared to MSM, suggesting that differences extend at least into the medium term.

2.4.2.3 ***Women vs MSW***

Six studies looked at differences in CD4 count response between women and MSW, of which all six were in Europe – five amongst those initiating ART and one amongst those on ART for at least six months. Three found poorer responses among MSW[126;364;367], two found no differences[361;368], and one found mixed results[362]. The study with mixed results was the RFHCS, which found that MSW had smaller increases in CD4 count at 12 months after ART initiation compared to women, but larger increases in CD4 count at 24 months[362]. This was despite similar median CD4 counts at ART initiation in these groups. Two studies from the same French cohort which had the same outcome of CD4 count increases >100 cells/μL, had conflicting results. In one, a greater proportion of MSW migrants and non-migrants had an absence of an 100 cells/μL CD4 count increase compared to migrant and non-migrant

women respectively[364]; however, others, which did not divide the population into migrants and non-migrants, found no evidence of differences between the groups[361]. These studies also had other differences that could account for the disparate results. The study that did not find differences between MSM and women: included individuals initiating ART rather than those on ART for at least six months; adjusted for calendar time; and did not adjust for ART adherence, AIDS at ART initiation, HCV diagnosis, drug use, depressive symptoms, or HIV care interruptions.

Table 2.5: Original research studies considering the association between CD4 outcomes and gender/sexual orientation among people prescribed ART [a b]

Publication Setting, date and study [c]	Study	CD4 count outcome definition	Prevalence of Gender/sexual orientation groups		Main results: Estimate (95% CI) [d]			Factors adjusted for
			Group	%	Measure	Unadjusted	Adjusted	
Longitudinal								
Barber, 2011, Antivir Ther[367] UK 1998-2007 UK CHIC	3,666 ART-naïve initiating ART	6 mths Change at 6 mths 1 yr Change at 1 yr	MSW Women MSW Women MSW Women MSW Women	41% 59%	Median (IQR) and mean difference	**230 (140-330)** **272 (170-397)p=0.0001** **108 (52-170),** **118 (54-192) p=0.003** **279 (179-380)** **310 (211-429)p=0.0001** 150 (80-231) 160 (81-248) p=0.16	n/k 0.0 +14.6 (+4.5, +24.6) n/k 0.0 +12.1 (-0.2, +24.4)	Age, ethnicity, ART regimen type, yr ART start, VL and CD4 at ART start, previous AIDS
Rosin, 2014, HIV Med[126] Switzerland 1998-2011 SHCS	3,925 ART-naïve initiating ART	Change at 1 yr	MSW women	50% 50%	Median (95% CI) and mean difference (95% CI)	**140 (64, 247)** **170 (78, 269)**	0.0 +17 (+5, +29)	Age, ethnicity, IDU, education, time, VL and CD4 at ART start, previous AIDS, HCV
Fardet 2006, HIV Med[361] France 1997-2001 ANRS	2,491 started ART during follow-up	Time to increase ≥100	MSM MSW WSM PWID other Women vs MSW	32% 20% 26% 10% 12%	HR	n/k	1.00 **0.86 (0.76, 1.00)** **0.83 (0.73, 0.95)** - - 0.97 (0.83,1.12)	Age, type of ART, VL and CD4 at study initiation, time
Lampe 2007, Arch Intern Med[365] UK 1999-2004	2,386 clinic population	Percent with <200 in calendar yr	MSM White MSW White women non-white MSW	63% 4% 5% 10%	RR	n/k	1.00 n/k n/k **2.38 (2.00, 2.94)**	Age, calendar period, time since first clinic visit

Publication Setting, date and study [c]	Study	CD4 count outcome definition	Prevalence of Gender/sexual orientation groups		Main results: Estimate (95% CI) [d]			Factors adjusted for
			Group	%	Measure	Unadjusted	Adjusted	
RFHCS			non-white women	17%			n/k	
Saunders 2015, HIV med[362] UK 2006-12 RFHCS	1,086 ART-naïve initiating ART	Change at 1 yr Change at 2 yrs	MSM MSW Women MSM MSW Women	52% 19% 29% 	Median (IQR)	**222 (113, 332)** **174 (83, 294)** **190 (108, 270)p<.0001** **278 (153, 407)** **274 (152, 408)** **266 (155, 378)p<.0001**	N/A	N/A
Thorsteinsson, 2012, BMC Infect Dis[368] Denmark 1997-2009 DHCS	908 initiating ART	1 yr 3 yrs 6 yrs	MSW Women MSW Women MSW Women	48% 52% 	Median	360 (220-510) 330 (210-457) 469 (318-656) 459 (316-600) 582 (382-793) 530 (380-696)	p=0.9 p=0.9 p=0.9	Age, ethnicity, period of ART initiation, previous AIDS diagnosis
Dray-Spira 2007, AIDS[364] France 2002-03 ANRS-VESPA	896 on ART for ≥6 mths	Absence of ≥100 increase between ART initiation and data collection	MSM French MSW French WSM migrant MSW migrant WSM PWID	38% 17% 10% 11% 11% 12%	% and OR	16.4% 10.6% 13.4% 27.4% 37.5% -	1.00 0.73 (0.39, 1.33) 0.93 (0.45, 1.91) **2.27 (1.14, 4.56)** **2.19 (1.17, 4.08)** **-**	Age, VL & CD4 at ART start, drug use, HCV, time on ART, diagnosis pre 1996, depression, HIV care interruptions, ART adherence [e]

Blue= MSM had improved CD4 outcomes than other gender/sexual orientation group; Red= MSW had improved CD4 outcomes than other gender/sexual orientation group; Green= Women had improved CD4 outcomes than other gender/sexual orientation group; **bold=** estimates with an associated P-value<0.05.

[a] Studies recruited not entirely before 2001, with sample size >100; [b] studies ordered by study size; [c] refer to list of relevant study acronyms on pages 10-11 for full study names; [d] estimates are standardised such that the MSM is the reference group; [e] adjusted for adherence which is on the causal pathway; MSM= men who have sex with men; MSW= men who have sex with women; WSM= women who have sex with men; PWID= people who inject drugs; yr/s=year/s; mths=months; HCV=hepatitis C virus; CI=Confidence Interval; OR=Odds Ratio; HR=Hazard Ratio; RR=Risk Ratio.

2.4.3 **ART non-adherence**

Seven studies examined the association between gender/sexual orientation and adherence to ART, four of which were cross-sectional and three longitudinal. The results of these are summarised in Table 2.6.

2.4.3.1 ***MSW vs MSM***

Of seven studies which considered differences in ART adherence between MSW and MSM, two found poorer ART adherence among MSW[357;373], while the remaining five found no evidence of differences[164;271;374-376].

In all four cross-sectional studies, ART non-adherence was defined by self-report. Three considered at least one measure which included schedule and/or instruction non-adherence in addition to missed doses[164;374;375]. A UK-based cross-sectional study found similar proportions of MSM and MSW reported ART non-adherence when doses, schedule and instructions were considered (56% and 54% respectively) and similar proportions of these groups self-reported at least two doses missed in the last week (8% and 12% respectively)[164]. None of the four studies found a substantially increased prevalence of non-adherence in MSW compared to MSM.

There were three longitudinal studies, two of which were from the US and considered an outcome measured using MEMS caps. The remaining study was based in Switzerland and considered self-reported adherence. One of the US-based studies found MSW had 15% lower adjusted adherence scores than MSM[373], while the other found no difference[271]. The study which found an association used the data from participants of a US-based RCT (where the intervention was not associated with improved adherence[377]). Given this cohort only included individuals currently using ART with a recent detectable VL the results are unlikely to be generalisable. The Swiss study was the only one to specifically consider previously naïve individuals starting ART. They found that heterosexuals had 59% increased odds of reporting ART non-adherence in the last four weeks, and single heterosexual migrants were three times more likely to report ART non-adherence compared to older MSM[357]. Adjustment for factors at ART initiation did not account for these differences.

2.4.3.2 ***Women vs MSM***

Women had poorer adherence to ART than MSM in four of seven studies[164;357;374-376239;331], with the other three finding no association. One[164] of four[374-376] cross-sectional studies considering self-reported non-adherence found an association.

All three longitudinal studies found that women had poorer adherence than MSM. One of two studies considering ART non-adherence measured by MEMS caps found that

women had 2.2% lower ART coverage over one month compared to MSM in unadjusted analyses[373]. However, following adjustment for demographic factors (including gender), SES, symptoms, and ART regimen, women had 3.8% higher ART coverage than MSM. This was likely the result of collinearity from gender being included in the model. In the other study, average adherence over one month was 76% among MSM and 74% among WSM[271]. However, a separate group of WSW had only 71% mean adherence. This study indicates that perhaps there may be differences in ART adherence by sexual orientation among women, but this study did not have a large enough sample of HIV-positive WSW to formally test this.

2.4.3.3 ***Women vs MSW***

Of five studies considering differences in ART non-adherence between women and MSW (four cross-sectional and one longitudinal) just one cross-sectional study found a greater prevalence of self-reported ART non-adherence among women[376], and the remaining four found no differences (three considered self-reported adherence[116;309;310], and one MEMS caps[271]). The study finding differences between the groups looked at self-reported adherence over a period of three days[376], whereas the other cross-sectional studies considered adherence over the period of a week[164;374;375]. Different measures of adherence may capture differing ART taking behaviours. In addition, the studies which did not find differences in adherence differed in several ways from the study which found women had poorer adherence: they were European studies rather than US-based; they considered combinations of dose, schedule and instruction adherence, rather than solely dose adherence; they had fewer study participants; and they considered less recent data.

Table 2.6: Original research studies considering the association between ART adherence outcomes and gender/sexual orientation among people prescribed ART [ab]

Publication, Setting, date and study [c]	Sample size	Non-adherence outcome		Prevalence of gender/sexual orientation groups		Main results [d e] Estimate (95% CI)			Factors adjusted for
		Self-report	Definition (prevalence)	Group	%	Measure	Unadjusted	Adjusted	
Cross-sectional									
Beer, 2014, AIDS Educ Prev[376] US 2009-10 MMP	3,606 on ART	Yes	<100% last 3 dys	MSM MSW WSM Other	48% 24% 25% 3%	%	**14% (12%, 16%)** **12% (9%, 15%)** **18% (15%, 20%)** **p=0.0038**	n/k	
Peretti-Watel 2006, Soc Sci Med[375] France 2003 ANRS-VESPA	1,809 on ART, diagnosed ≥1 yr	Yes	<100% dose or schedule last wk (42%)	MSM MSW WSM	44% 34% 23%	%	41.5% 40.8% 44.9% p=0.40	n/k	
Sherr 2008, AIDS Care[374] UK 2005-06 5 centres	502 on ART	Yes	100% dose but <100% schedule or instruction last wk (36.1%) <100% schedule dose, or instruction last wk (22.4%)	MSM MSW WSM MSM MSW WSM	64% 12% 23%	%	35.9% 35.1% 37.6% 20.9% 21.1% 21.1%	n/k	
Sherr 2010, AIDS Care[164] UK 2005-06 5 centres	486 on ART	Yes	<100%, schedule dose or instruction last wk (57.2%) ≥1 dose missed last wk (21.0%) ≥2 doses missed last wk (10.1%)	MSM MSW WSM MSM MSW WSM MSM MSW WSM	67% 12% 21%	%	56.4% 54.4% 59.4%; p=0.80 20.9% 19.3% 21.8%; p=0.93 8.4% 12.3% 13.9%; p=0.24	n/k	

Publication, Setting, date and study [c]	Sample size	Non-adherence outcome		Prevalence of gender/sexual orientation groups		Main results [d e] Estimate (95% CI)			Factors adjusted for
		Self-report	Definition (prevalence)	Group	%	Measure	Unadjusted	Adjusted	
Longitudinal									
Keiser 2013, AIDS Behav[357] Switzerland 2000-08 SHCS	1,485 ART-naïve initiating ART	Yes	<100% last 4 wks	older MSM young MSM MSW and WSM older MSW PWID single migrants migrant women in partnership MSM (all) Heterosexual (all)	35% 4% 20% 10% 13% 10% 9% 1.00 **1.59 (1.11, 2.22)**	OR	1.00 2.00 (0.89, 4.55) **1.69 (1.11, 2.56)** 0.90 (0.49, 1.67) - **2.94 (1.75, 5.00)** 1.30 (0.70, 2.38) 1.00 **1.59 (1.11, 2.22)**	1.00 2.00 (0.88, 4.55) **1.79 (1.16, 2.78)** 0.93 (0.50, 1.72) - **3.23 (1.85, 5.56)** 1.30 (0.70, 2.44) 1.00 **1.61 (1.14, 2.27)**	Age, type of ART regimen, VL and CD4 at study enrolment, stage of disease Additionally adjusted for gender
Remien 2014, AIDS Behav[271] US 1997-2009 MACH14	459 on ART	No	MEMS: Mean coverage over 1 mth (mean=0.75 SD=0.28)	MSM MSW WSM WSW	34% 29% 16% 5%	Mean (SD)	0.76 (0.28) 0.75 (0.29) 0.74 (0.25) 0.71 (0.28)	n/k	
Genberg 2013, AIDS patient care STDs[373] US 2002-05 RCT (two centres)	137 on ART, detectable VL at most recent clinic visit	No	MEMS: % time covered by ART in 30 dys after study visit	Women M/WSM M/WSW MSW vs MSM Women vs MSM	22% 58% 13%	Mean difference (SE)	 **-19.0 (6.4)** **-2.2 (6.4)**	 **-14.8 (8.0)** **3.8 (7.1)**	Gender, age, ethnicity time, education, marital status, employment, ART type, depression, mental score, physical score, stage of change [f]

Blue= MSM had better ART adherence than other gender/sexual orientation group; Red= MSW had better ART adherence than other gender/sexual orientation group; Green= Women had better ART adherence than other gender/sexual orientation group; **bold=** estimates with an associated P-value<0.05.

[a] Studies recruited not entirely before 2001, with sample size >100; [b] studies ordered by study size within each category (cross-sectional and longitudinal); [c] refer to list of relevant study acronyms on pages 10-11 for full study names; [d] estimates are standardised such that the MSM is the reference group; [e] standardised such that non-adherence is the outcome; [f] stage of change= model for changing behaviour; MSM= men who have sex with men; MSW= men who have sex with women; WSM= women who have sex with men; WSW= women who have sex with women; PWID= people who inject drugs; n/k=not known; mth=month; wk/s=week/s; dys=days; CI=Confidence Interval; SE=Standard Error; SD=Standard Deviation; OR=Odds Ratio; MEMS=Medical Event Monitoring System;

2.4.4 **Discussion – Association between treatment outcomes and gender/sexual orientation**

This review found improved ART responses among MSM compared to MSW in 10/12 studies of virological response to ART and 4/4 studies of CD4 count outcomes. Likewise, MSM had improved virological and CD4 count outcomes compared to women in 6/11 and 3/3 studies, respectively. No studies found that MSM had a poorer response. While some observed differences are relatively small[360], others found relative risks in the range of 2-3[362;364;365]. There was less agreement when comparing MSW and women[126;362;367]. One study found that women had poorer virological responses to ART after adjustment, and five found no difference. In contrast, three studies found they had improved CD4 count responses, and three found no difference. There were no obvious reasons for these differences, although adjustment for baseline factors frequently attenuated the differences observed in unadjusted analyses[126;367]. This highlights the important role of other factors, such as ethnicity, migrant status, having children, and SES. This last point will be further explored in Chapter 8.

There were more mixed findings when considering the outcome of adherence. It is feasible that the observed gender/sexual orientation differences in treatment response were not a result of differences in adherence to ART, and other factors were playing a role such as drug resistance and pharmacokinetics. However, the only study, which considered both virological, and adherence outcomes found that MSM had consistently improved outcomes. Furthermore, only one studied adherence among individuals initiating first-line ART and found differences between the three groups[357]. It is possible that initial adherence to ART could differ but be similar in the longer term; further study of adherence levels amongst those initiating ART and according to time spent on ART is required. Reasons for any differences between groups could include: younger age, alcohol abuse, financial difficulty and unsatisfactory housing[375]. The ANRS study suggested that predictors might also be context-specific: food privation, migrant status and discriminatory behaviour from relatives were only predictive of non-adherence among heterosexual individuals; and duration since diagnosis, suicide attempts and IDU only among MSW. Thus, different interventions may be required in different gender/sexual orientation groups. Finally, it is possible that any observed differences between gender/sexual orientation groups could relate to different perceptions of adherence and social desirability bias

Treatment modification, i.e. switching or discontinuing ARVs or the entire ART regimen, was a suggested option for individuals with incomplete virological suppression (treatment failure)[378], or drug toxicities. However, it may also indicate compliance issues. Discontinuing ART for any period of time could lead to virological

rebound, drug resistance and/or progression to AIDS and death[162]. Studies have reported higher rates of treatment switches during the first year of treatment[362] and higher rates of complete ART discontinuation[300;321] among women compared to men, even when pregnant women have been excluded[126]. In the RFHCS, toxicity and treatment choice were common reasons given for switching regimen among all gender/sexual orientation groups but treatment failure and pregnancy-related reasons were more common for MSW and women, respectively[362]. Similarly, an Italian study[189] and a Dutch study[341] found women were at a higher risk of toxicity-related outcomes. Even in studies where men and women have similar rates of discontinuation, women are more likely to report adherence difficulties as their reason for stopping treatment[379].

Ethnicity is an important consideration alongside gender/sexual orientation, since they are usually highly correlated in HIV-positive populations. Four of 15, 2/7 and 1/7 studies with virological, CD4 count and adherence outcomes respectively considered ethnicity/migrant status and gender/sexual orientation as a combined variable; an additional six, three and one provided estimates adjusted for ethnicity. Adjustment can help to identify the extent to which any differences in ART-response between gender/sexual orientation groups operate through ethnicity. However, if, as one would expect, ethnicity is very highly correlated with gender/sexual orientation, it may not be possible to distinguish between the effects of gender/sexual orientation and ethnicity.

Few studies provided information on pregnancy. The characteristics of HIV-positive pregnant women are different to those of men and non-pregnant women on ART, due to different recommended ART regimens[50;281], closer monitoring[51;290], earlier HIV diagnosis due to opt-out antenatal testing and immediate ART start regardless of current CD4 count[217-219]. Four studies explicitly performed sensitivity analyses excluding pregnant women and three then found no differences in virological outcome compared to men[330;380;381]. In contrast, although the primary analysis of the UK CHIC study found no difference between women and MSW, the latter group were at a higher risk of virological rebound after excluding pregnant women[367]. Furthermore, women may experience higher levels of virological rebound[372], or historically may completely discontinue ART if they only initiated treatment for prevention of mother-to-child transmission[282]. Prior studies have also shown that caring for two or more children can have a negative impact on ART response for women[382], likely due to difficulty in adhering to ART with greater care-giving responsibilities[382;383].

My review had a few limitations. Since gender refers to the social or cultural categorisation of men and women, it is conceivable that differences in treatment

response between the gender/sexual orientation groups may not be generalisable across social or cultural settings. Gender/sexual orientation was not the primary covariate of interest in many studies, thus only solely unadjusted or adjusted results were available. Inconsistent outcome definitions, particularly for adherence[384;385], across studies make it difficult to make direct comparisons of associations or to combine them into a pooled estimate. In one study, individuals were not necessarily all on ART and a small proportion were on fewer than three ARVs, although the CD4 count of untreated individuals and the percentage receiving fewer than three ARVs did not vary between gender/sexual orientation groups[365].

Publication bias was likely to be a concern because studies finding no association, or an unexpected inverse association, may have been less likely to publish or to note their findings in their publication. There is evidence that, in the general population, women are more likely to self-report poorer health, particularly women of black ethnicity[386]. Differences in adherence between the groups could be a result of differences in reporting bias. Selection bias could be induced by studies using MEMS caps since pillboxes may not have been able to be used by all individuals[387] and/or flexibility and privacy of pill-taking may have been compromised[388]. There may be some unmeasured confounding present due to observational study designs.

Thus, my review suggests that it is still unknown whether there are gender/sexual orientation disparities in adherence and response to ART. There are also several understudied areas, for example European studies considering gender/sexual orientation disparities. In addition, of the studies identified by this review, only one from the RFHCS (the same database I have analysed in my thesis) considered differences between MSM, MSW and women in virological rebound in addition to virological suppression[362]. Three had a study period which ended over 10 years ago[361;364;365], and although one study found similar reductions in prevalence of ART non-response over calendar time in each gender/sexual orientation group[365], there are no recent studies. These trends may have changed in recent years following the advances in ART regimens and increased awareness of the importance of ART adherence. Additional study of trends over time would provide insight into whether current strategies are sufficient to lead to reduction or elimination of inequalities in ART response by gender/sexual orientation in the near future. Although adherence is likely to be a key determinant of differences in virological response to ART, only one study observed both outcomes[357] and two considered virological response adjusted for ART adherence[359;364]. Satisfying this gap in the literature would likely give insight into possible adherence interventions to reduce disparities by gender/sexual orientation in ART response.

2.5 **Review of the literature on socio-economic status and HIV treatment outcomes**

This chapter has so far focused on the differences in HIV treatment outcomes and ART adherence by gender and sexual orientation. This section assesses socio-economic differences in virological outcomes, CD4 count responses and in ART adherence. To my knowledge, there is no recent systematic review of this topic. Socio-economic factors are structural factors, i.e. those characterised by social institutions such as family, education, religion, and economic and political institutions. Both structural[389-392] and behavioural[393-397] factors have been shown to play a role in shaping health inequalities. Prior studies have suggested that structural factors are the most important determinants of health[398], as they operate both independently and through their influence on lifestyle[399]. Social structural factors (higher income, working full-time, caring for a family and social support) have been found to be more important determinants of women's health than men's, and behavioural factors (smoking and alcohol consumption) were more important for men[398].

2.5.1 **Virological and immunological response to ART**

Seventeen studies looked at the association between SES and virological response (Table 2.7). Seven studies considered SES and CD4 count response (Table 2.8).

2.5.1.1 ***Education***

Educational achievement was the most frequently available measure of SES in large observational studies, categorised as either highest level of education attained (for example 'university degree') or number of years in education. Since number of years of education does not contain any information on qualifications achieved, highest level of education may be a better measure. However, qualifications could be difficult to compare between settings, e.g. A-level in the UK with the baccalaureate in France.

Four cross-sectional studies[359;400-402] and five longitudinal studies[126;403-406] considered the association between education and virological non-suppression among ART-treated individuals. Of these, four found lower education level was associated with lower odds of VL suppression (aOR=0.2-0.6)[359;402;403;405], two found weak evidence of this association (aOR=0.9 in both)[126;401], and two found no association[404;406]. The remaining study, the Veterans Aging Cohort Study (VACS), found weak evidence that lower education was associated with improved virological response[400]. The individuals included in this study tended to be of an older age (median age 49 years) and only 2% were women, compared to the other studies that all had a lower mean or median (33-48) age and higher percentages (14-32%) of women. Two of the studies which found either weak evidence or no evidence of an association were conducted among specific

subgroups: among food insecure individuals[401] and in a cohort of PWID[404], groups in which there may be less variation in educational level. Importantly, one of these studies only reported analyses adjusted for other socio-economic factors, and so collinearity may have accounted for the lack of association[401].

Two studies found no evidence of an association between educational attainment and virological rebound among those with virological suppression on ART[407;408]. Another found no statistically significant association between education and change in VL over time[409]; with all estimates close to one. One potential explanation for the disparate findings for VL rebound compared to VL suppression may relate to the fact that those who achieve initial virological suppression may be less affected by the mechanisms acting against maintaining virological suppression, such as non-adherence.

One cross-sectional study and five longitudinal studies considered education and CD4 count response to ART (Table 2.8). Two found that lower educational attainment was associated with poorer response[403;405] and four reported no association[126;400;406;409], although they did not provide further information. Three studies that found no association considered absolute changes in CD4 count[126;406;409] and the other considered whether CD4 count was <200 cells/μL at the time of the study among individuals on ART[400]. In contrast, the two studies that found lower odds of CD4 response to ART among those with lower educational attainment, both defined the outcome as CD4 increases of less than 50 or 100 cells/μL after six months of first-line ART[403;405].

2.5.1.2 ***Employment***

Employment may be used as a measure of SES as a binary (employed vs. not employed) or categorical variable (e.g. full- or part-time status and/or reasons for non-employment, such as retirement, illness). Use of a binary categorisation could lead to loss of information, such as how those who are unemployed due to inability to work differ from others. Type of occupation is also sometimes used instead of employment status.

Of the six studies identified which considered the association between employment status and virological suppression/non-suppression, four were cross-sectional[359;400-402] and two were longitudinal[342;404]. Three studies found that unemployment was associated with poorer virological response to ART in adjusted analyses[342;359;401], one found this association in unadjusted analyses only (OR=1.85)[402], and two found no evidence of an association[400;404], with estimates close to one. No studies found that unemployment was associated with improved response to ART. The French ANRS

study also considered the association between occupation and six months of sustained virological suppression among individuals on ART[359]. The greatest difference was between the tradesperson and executive groups (OR=0.6), but, likely due to lack of numbers in each group, there were relatively wide confidence intervals. One additional study found that unemployed individuals had smaller improvements in VL following ART initiation than employed individuals[409].

Across the studies considered, the prevalence of unemployment ranged from 13% to 95%. The studies with the lower prevalence of unemployment found it had the greatest effect on virological outcome[342;359]. The distribution of employment status in the study populations is likely to affect their ability to detect any differences between groups. In addition, one of the studies which did not find an association between employment and virological non-suppression was among PWID, a group in which other factors might have dominated in determining response to ART[404]. Three of the four US-based studies found non-employment was associated with poorer VL outcome[401;402;409]. It might be expected that stronger adverse effects of non-employment on ART response would be apparent in a setting without a nationalised health system, where an individual's employment status is likely to be strongly associated with health insurance status, and therefore potentially access to care and treatment.

Two studies were identified that assessed CD4 count outcomes, one of which was cross-sectional[400] and the other longitudinal[409]. Both of these US-based studies found that unemployment was associated with poorer immunological response to ART.

2.5.1.3 *Income/financial status*

Income might be regarded as a desirable indicator of SES since it is a direct measure of material living standards and ability to access resources. Some studies consider absolute income as a categorical variable, while others consider the extremes of financial status, such as financial insecurity or hardship. Studies considering income level may use either individual or household income. The latter may be more reflective of living standards.

Of the three studies investigating the association between income and virological non-suppression or change in VL, two cross-sectional[400;401] and one longitudinal[409], none found an association. However, in another study solely among women, the Women's Interagency HIV study (WIHS), lower income was associated with an 80% higher adjusted rate of rebound[408]. All four of the studies investigating income as a covariate were based in the US. One may expect that income would be an important factor in more than one of these studies since they were all in a setting without universal free

access to care. However, the participants of these studies were those who had access to ART in the first place, thus they represented a subset of low income PLWH.

In addition to the studies looking at income level, four cross-sectional studies considered deprivation measures. Three of these studies considered the association between food insecurity as a marker of deprivation and virological non-suppression[400;401;410], and the other study considered the association of material deprivation defined using the EU-SILC questionnaire[411] with sustained virological suppression[359]. Three studies found evidence of an association between greater deprivation and poorer virological response at least in unadjusted analyses (OR=1.4-1.7)[359;400;410], and the other study only displayed adjusted associations[401]. In adjusted analyses, all four included other socio-economic factors in the model, so associations/lack of association between deprivation and VL response in these models could be affected by collinearity. In the VACS, food deprivation was associated with 37% higher adjusted odds of VL >500 copies/mL, despite adjustment for other socio-economic factors and despite finding no differences in this outcome by absolute income[400].

All three studies of immunological ART response and income/deprivation found an association between poorer financial status, measured by lower monthly income (OR=1.4 or 24 cells/μL lower improvement)[400;409] and food insecurity (OR=1.5-1.6)[400;410], and poorer CD4 count response in unadjusted analyses.

2.5.1.4 ***Housing***

There is a relatively high prevalence of HIV among homeless individuals in some countries[412], thus housing status may be an important factor to consider for HIV treatment outcomes. A number of studies have categorised housing status as homeless or housed. Others use housing stability and consider types of housing situation such as homeowner, renting, or living with relatives.

Poorer housing status was associated with VL non-suppression in all three of the studies which assessed this (two cross-sectional (OR=1.4-2.4)[400;402], one longitudinal (time to suppression HR=0.6)[404]) in unadjusted analyses. The longitudinal AIDS Care Cohort to evaluate Exposure to Survival Services (ACCESS) study also found 40% lower adjusted rate of suppression among homeless individuals[404]. However, both of the cross-sectional studies included multiple socio-economic factors in multivariate analyses; therefore, again collinearity may have been an issue[400;402].

One further study in the ACCESS cohort considered VL rebound and found no evidence of an association, with an unadjusted HR of 0.9 comparing unstable housing

to stable housing[407]. On the other hand, a qualitative study of 27 individuals with histories of illegal drug use from the same cohort identified changes in housing status and neighbourhood of residence were associated with virological rebound[413]. Perhaps the disruption from changes in circumstances and greater distances from usual health care providers may have been influential for VL response rather than housing status.

In the only study that assessed immunological outcomes and homelessness, VACS, recently homeless individuals on ART had twice the odds of having a CD4 count ≤200 cells/μL compared housed individuals[400].

2.5.1.5 *Health insurance*

In settings where healthcare and treatment are not free at the point of use, health insurance, like income, can act as a direct marker of SES. Insurance may be considered as a binary variable, or as three levels: none, public and private insurance.

Three longitudinal US-based studies considered the association between health insurance status and virological ART response[343;363;408]. In unadjusted analyses (in studies where this was available) a lower rate of virological suppression (HR=0.8)[363] and a higher rate of virological rebound (HR=1.6)[408] were observed among those with public compared to private insurance. However, there was evidence that uninsured individuals had 0.7 times the rate of rebound compared to privately insured individuals. In adjusted analyses there was no evidence that virological response differed between individuals with public or private insurance[363;408], but adjustment reversed the association between none vs. private insurance, such that those with no insurance had 46% increased rate of rebound[408]. In the Community Health And Safety Evaluation (CHASE) study there was no evidence of an association between insurance and virological rebound, however, it reported adjusted analyses only (aHR=1.3)[343].

2.5.1.6 *Neighbourhood SES*

Neighbourhood SES differs from all other SES measures considered, as it is not an individual-level factor. There is mixed evidence for the use of neighbourhood-level data as a proxy for individual-level SES[285;414]. The most important disadvantage of these measures is that, by definition, inferences for an individual are made based on group data. There is a high risk of misrepresenting an individual's SES in settings where large variations in socio-economic circumstance exist within "neighbourhoods."

In the SHCS, among individuals initiating ART, those in the lowest quintile of a national index of socio-economic position had 44% lower odds of VL suppression after six months compared to the highest quintile[415], in a model adjusted for demographic factors.

Table 2.7: Original research studies considering the association between virological outcomes and socio-economic factors among people prescribed ART [a b]

Publication Setting, date and study [c]	Sample size	Outcome: Viral response	Measures of SES		OR (95% CI) Yes vs No [d]		Factors adjusted for
		Definition	Marker	Prevalence	Unadjusted	Adjusted	
Cross-sectional							
Wang, 2011, J Gen Intern Med[400] US 2002-08 VACS	1,911 receiving ART	>500 study enrolment (39%)	Education <high school Non-employed Annual income<$25,000 Food insecurity Homeless in last 4 wks Food insecurity	7% 74% 74% 24% 10% 	0.68 (0.45, 1.08) 1.11 (0.90, 1.37) 1.09 (0.89, 1.36) **1.49 (1.17, 1.81)** **1.41 (1.03, 1.94)** 	0.75 (0.47, 1.19) - - **1.37 (1.09, 1.73)** 1.15 (0.82, 1.63) 1.32 (1.05, 1.68)	Age, ethnicity, relationship status, recent homelessness/food insecure, cocaine use, depression score Additionally adjusted for ART adherence [e]
D'Almeida, 2016, Antivir Ther[359] France 2011 ANRS- VESPA2	1,246 ART-naïve, on ART ≥1 yr	<50 for >6 mths at time of survey (78%)	Education<primary Unemployed Manual worker Material deprivation	21% 14% 24% 30%	**=0.6 (0.3, 1.0)** (vs >2 yrs university) **0.5 (0.3, 0.8)** 0.8 (0.4, 1.3) (vs executive) **0.6 (0.4, 0.8)**	**0.4 (0.2, 0.9)** (vs >2 yrs university) **0.6 (0.3, 1.0)** 1.5 (0.8, 2.9) (vs executive) 1.0 (0.7, 1.9)	Gender/sexual orientation, age, other SES factors, HBV, HCV, health literacy, social network, CD4 at ART start, time on ART, depressive symptoms, CVD, anxiety symptoms, ART adherence, HIV discrimination [e]
Kalichman, 2015, J Community Health[410] US 2012 Single centre	521 prescribed ART	Most recent detectable (16%)	food insecurity last mth	38	1.4 (0.80, 2.61)	1.3	Housing, transportation, neighbourhood poverty, living in an area without a supermarket

Publication Setting, date and study [c]	Sample size	Outcome: Viral response	Measures of SES		OR (95% CI) Yes vs No [d]		Factors adjusted for
		Definition	Marker	Prevalence	Unadjusted	Adjusted	
Kalichman, 2015, Infect Dis Ther[401] US 2013-14 Multi-centre	418 food insecure on ART	Most recent >200 (23%)	Yrs of education Non-employed Annual income<$10,000 Food insecurity factors	- 87% 68% -	n/k	0.89 (0.76, 1.03) /year longer **1.39 (1.05, 1.85)** 1.10 (0.74, 1.64) 1.08 (0.93, 1.25) /additional factor	Yrs since diagnosis, alcohol and drug use, side-effects, medication necessity and concern beliefs, ART food requirements, other SES factors
Shacham, 2010, AIDS Pat Care STDS[402] US 2007 Single centre	370 on ART	>400 (11%)	Education ≤ high school e Unemployed Homeless	49% 59% 8%	**3.23 (1.58, 6.58)** **1.85 (1.11, 3.85)** **2.42 (1.45, 8.46)**	**2.32 (1.08, 5.00)** NS NS	Gender, age, employment status, PI- or NNRTI-based ART
Longitudinal							
Rosin, 2014, HIV Med[126] Switzerland 1998-2011 SHCS	3,925 ART-naïve initiating ART heterosexual	<50 at 12 mths (77%)	Length of education<9 yrs	12%	**0.80 (0.69, 0.93)**	0.89 (0.75, 1.07)	Gender, age, ethnicity, IDU, prior-AIDS, HCV, VL and CD4 at ART start, ART regimen, time
Gueler, 2015, AIDS[415] Switzerland 2000-13 SHCS	2,694 ART-naïve initiating ART	<50 at 6 mths	Lowest neighbourhood SES quintile	23%	n/k	**0.66 (0.49, 0.88) (vs. highest quintile)**	Gender, age
Saracino 2016, Clin Microbiol Infect[342] Italy 2004-14 ICoNA	2,321 ART-naïve initiating ART >6 mths ago	Time to two consecutive >200 (3.3 /100 person yrs)	Education ≤primary Unemployed	6% 13%	n/k	- **2.09 (1.31, 3.32)** [z]	Gender, migrant status, CD4 at enrolment, CDC stage at enrolment, initial ART regimen

Publication Setting, date and study [c]	Sample size	Outcome: Viral response	Measures of SES		OR (95% CI) Yes vs No [d]		Factors adjusted for
		Definition	Marker	Prevalence	Unadjusted	Adjusted	
Sobrino-Vegas, 2012, Antivir ther[405] Spain 2004-09 CoRIS	1,903 ART-naïve initiating ART	<50 at 6 mths (76%) <50 at 1 yr (80%)	Education ≤primary Education ≤primary	45%	**0.51 (0.37, 0.68)** **0.53 (0.41, 0.69)**	**0.56 (0.38, 0.82)** 0.75 (0.55, 1.03)	Mode of HIV acquisition, gender, age, VL and CD4 at ART start
Legarth, 2014, AIDS[406] Denmark 1998- 2009 DHCS	1,178 ART-naïve initiating ART	Time to <500	Low education from attainment register	29%	NS	n/k	
Novak 2015, JAIDS[363] US 2000-13 HOPS	926 ART-naïve initiating ART	Time to <500	Public insurance	46%	**0.8 (0.7, 1.0)** [x]	0.9 (0.8, 1.1) [x]	Gender/sexual orientation, age, ethnicity, IDU, private/public clinic, date diagnosis, VL and CD4 at ART start
McFall, 2013, JAIDS[408] US 2006-11 WIHS	887 women on ART, confirmed VL<80, in care >3 yrs	Time to >200	Education <high school Annual income ≤$24,000 Non home owner Public insurance No insurance	37% 68% 12% 16%	1.16 (0.92, 1.49) [x] **1.75 (1.30, 2.36) [x] (vs. ≥$36,001)** **1.59 (1.22, 2.08) [x] (vs. private)** **0.71 (0.54, 0.94) [x] (vs. public)**	**1.80 (1.19, 2.72)** [x] - - 0.83 (0.57, 1.22)[x] (vs private) 1.46 (0.98, 2.16)[x] (vs public)	Age, CD4 at previous visit, previous AIDS diagnoses, time since ART initiation, VL>200 prior to study, clinic
Pence, 2008, JAIDS[343] US 2001-02 CHASE	474 on ART, VL<400 at enrolment	Time to ≥400	No insurance	21%	n/a	1.25 (0.67, 2.38) [x] (Public/none vs. private)	Gender, age, ethnicity, time on ART regimen, first-line ART, depression, alcohol, drug

Publication Setting, date and study [c]	Sample size	Outcome: Viral response	Measures of SES		OR (95% CI) Yes vs No [d]		Factors adjusted for
		Definition	Marker	Prevalence	Unadjusted	Adjusted	
							use, trauma, recent stress, social support, self-efficacy
Zaragoza-Macias, 2010, AIDS Res Hum Retroviruses[403] US 2003-05 Single centre	287 ART-naïve initiating ART	<400 wk 24 (73%) <400 wk 48 (72%)	Education <high school Education <high school	29% 	n/k n/k	1.69 (0.29, 10.00) **0.20 (0.04, 0.90)**	Gender, age, ethnicity, ART regimen, VL and CD4 at ART start, ART adherence [e]
Milloy, 2012, JAIDS[407] Canada 1996-2009 ACCESS	277 PWID on/initiating ART, 2 consecutive VL<500/<50	Second of two VL>1000 (45%)	Education <high school Unstable housing	n/k	1.04 (0.88, 1.24) [x] 0.90 (0.76, 1.06)	n/k	
Milloy, 2012, AIDS Patient Care STDS[404] Canada 1996-2009 ACCESS	247 PWID ART-naïve initiating ART	Time until <500 (57% ≥1 VL suppression)	Education <high school Non-employed; >1 episode homelessness >1 episode homelessness	39% 95% 42% 	0.89 (0.76, 1.05) [x] 1.11 (0.84, 1.47) [x] **0.56 (0.40, 0.78)** [x]	- - **0.60 (0.43, 0.84)** [x] 0.79 (0.56, 1.11) [x]	Age, recent incarceration, yr ART start, VL at ART start Additional adjustment for ART adherence [e]
Simoni, 2013, AIDS care[409] US 2003-07 Single centre RCT	224 ART-naïve/ restarting/ switching	Trajectory 0 to 3 mths after ART start	Education ≤high school Non-employed Income<$552/mth	21% 80% ~50%	-0.39 log copies/mL[y] +0.07 log copies/mL[y] +0.14 log copies/mL[y]	N/A	N/A

Publication Setting, date and study [c]	Sample size	Outcome: Viral response	Measures of SES		OR (95% CI) Yes vs No [d]		Factors adjusted for
		Definition	Marker	Prevalence	Unadjusted	Adjusted	
	new ART regimen	Trajectory 3 to 9 mths after ART start	Education ≤high school Non-employed Income<$552/mth		+0.48 log copies/mL[y] -0.32 log copies/mL[y] -0.08 log copies/mL[y]		

Red= virological outcomes of higher SES group were better than those of lower SES group, Green= virological outcomes of lower SES group were better than that of higher SES group; **bold=** estimates with an associated P-value<0.05.

[a] Studies recruited not entirely before 2001, with sample size >100; [b] studies ordered by study size within each category (cross-sectional and longitudinal); [c] refer to list of relevant study acronyms on pages 10-11 for full study names; [d] estimates are standardised such that the lower SES group is compared with the higher one; [e] adjusted for adherence which is on the causal pathway; [x] hazard ratio rather than odds ratio presented; [y] mean difference rather than odds ratio presented; [z] risk ratio rather than odds ratio presented; SR= self-reported; NS= non-significant association if estimates not given; n/k=not known; N/A=not applicable; yr/s=year/s; mth/s=month/s; wk/s=weeks; CI=Confidence Interval; OR=Odds Ratio; PWID= people who inject drugs; IDU= injection drug use; HCV=Hepatitis C virus; HBV=Hepatitis B virus; CVD=Cardiovascular disease.

Table 2.8: Original research studies considering the association between CD4 outcomes and socio-economic factors among people prescribed ART [a b]

Publication Setting, date and study [c]	Study	CD4 count outcome definition (cells/mm^3)	Prevalence of socio-economic groups		Estimate (95% CI) [d]		Factors adjusted for
			Group	%	Unadjusted	Adjusted	
Cross-sectional							
Wang, 2011, J Gen Intern Med[400] US 2002-08 VACS	1,860 receiving ART	≤200 (24%)	Education<high school	6%	1.01 (0.60, 1.69) (vs college graduate)	-	Age, ethnicity, relationship status, other SES factors, binge alcohol use, Cocaine use, opioid use, depression score
			Non-employed	74%	**1.82 (1.37, 2.38)**	**1.75 (1.30, 2.38)**	
			Annual income<$25,000	74%	**1.39 (1.08, 1.82)**	1.09 (0.80, 1.45)	
			Food insecure in past 4 wks	24%	**1.45 (1.14, 1.86)**	1.13 (0.86, 1.47)	
			Homeless in past 4 wks	10%	**2.00 (1.45, 2.57)**	**1.66 (1.15, 2.38)**	
			Non-employed			**1.72 (1.28, 2.38)**	
			Homeless in past 4 wks			**1.63 (1.13, 2.34)**	Additionally adjusted for ART adherence [e]
Kalichman 2015, J Community Health[410] US 2012 Single centre	521 prescribed ART	Most recent <500 (54%)	Food insecure in last mth	38%	**1.6 (1.04, 2.62)**	1.4	Housing, transportation, neighbourhood poverty, food desert
Longitudinal							
Rosin, 2014, HIV Med[126] Switzerland 1998-2011 SHCS	3,925 heterosexuals ART-naïve initiating ART	Median increase from ART initiation to 1 yr	Length of education <9 yrs	12%	n/k	NS	Gender, age, ethnicity, IDU, prior AIDS, HCV, VL and CD4 at ART start, ART type, calendar period

Publication Setting, date and study [c]	Study	CD4 count outcome definition (cells/mm^3)	Prevalence of socio-economic groups		Estimate (95% CI) [d]		Factors adjusted for
			Group	%	Unadjusted	Adjusted	
Sobrino-Vegas, 2012, Antivir ther[405] Spain 2004-09 CoRIS	1,903 previously ART-naïve initiating ART	>50 increase in 0-6 mths (82%) >50 increase in 6-12 mths (74%)	Education ≤ primary	45%	**0.56 (0.41, 0.76)** **0.42 (0.30, 0.59)**	**0.71 (0.50, 1.00)** **0.57 (0.40, 0.82)**	Mode of HIV acquisition, gender, age, VL and CD4 at ART start
Legarth, 2014, AIDS[406] Denmark 1998-2009 DHCS	1,178 previously ART-naïve initiating ART	Median increase at 12 wk intervals	Low Education from attainment register	29%	NS	n/k	
Zaragoza-Macias, 2010, AIDS Res Hum Retroviruses[403] US 2003-05 Single centre	287 previously ART-naïve initiating ART	Increase>100 by wk 24 (56%) Increase>100 by wk 48 (72%)	Education <high school Education <high school	29%	n/k n/k	**0.20 (0.04, 0.99)** 0.65 (0.13, 3.23)	Gender, age, ethnicity, ART regimen, VL and CD4 at ART start, adherence [e]
Simoni, 2013, AIDS care[409] US 2003-07 Single centre RCT	224 ART-naïve/ restarting/ switching new ART regimen	CD4 trajectory over 9 mths from ART initiation	Education ≤high school Unemployed Income <$552/mth	21% 80% ~50 %	-4 cells/µL p=0.16 [y] **-30 cells/µL [y] p=0.003** **-24 cells/µL [y] p=0.003**	N/A	N/A

Red= CD4 outcomes of higher SES group were better than those of lower SES group, Green= CD4 outcomes of lower SES group were better than that of higher SES group; **bold**= estimates with an associated P-value<0.05.

[a] Studies recruited not entirely before 2001, with sample size >100; [b] studies ordered by study size within each category (cross-sectional and longitudinal); [c] refer to list of relevant study acronyms on pages 10-11 for full study names; [d] estimates are standardised such that the lower SES group is compared with the higher one; [e] adjusted for adherence which is on the causal pathway; [y] mean difference rather than estimate and 95% CI; SR= self-reported; RCT= Randomised Controlled Trial; IDU= intravenous drug use; HCV= Hepatitis C; NS= non-significant association if estimates not given; n/k=not known; N/A=not applicable; yr/s=year/s; mth/s=month/s; wk/s=weeks; CI=Confidence Interval; OR=Odds Ratio; PR=Prevalence Ratio; HR=Hazard Ratio.

2.5.2 **ART non-adherence**

In general, the findings for an association between poorer levels of SES markers and increased risk of ART non-adherence were more mixed than those seen for VL and CD4 outcomes (Table 2.9, where a red result indicates poorer adherence among those of lower SES and green indicates the opposite association).

2.5.2.1 ***Education***

Again, the most common marker of SES available was educational level for which, out of 25 studies: 11 found that lower educational attainment was associated with non-adherence[346-349;353;354;374;402;416-418]; 11 did not find evidence of an association[164;350;373;401;419-425]; two found weak evidence of better adherence among individuals with lower educational attainment[426;427]; and one UK study found that, among women, having below university level education was associated with 75% lower odds of ART non-adherence[428].

In the UK study, which found an inverse association between education and non-adherence in the subgroup of women compared to the subgroup of men, the authors suggest that this could potentially be explained by less trust of health-care professionals among highly educated women[428]. However, there was little evidence of why highly educated women would be more mistrustful than highly educated men in the literature. Two other UK-based studies did not find an association between adherence and education[164;374], however, they did not consider men and women separately. In these studies the definition of adherence was also more stringent – <100% dose, schedule and instruction adherence was defined as non-adherence – and as such different lifestyle factors may have been more important in explaining non-adherence than education. In studies considering these three aspects of non-adherence separately, less education was not associated with dose non-adherence, but instead with greater odds of self-reported instruction[418] or schedule[347] non-adherence. This suggests that lower levels of education may have been associated with greater difficulties in taking ART at the scheduled times or as instructed, but not necessarily with missing doses altogether.

Although there were mixed findings for whether education was associated with non-adherence using most adherence measures, unannounced telephone pill-count consistently found no association between education and adherence[401;419;420]. This may have been due to more accurate measurement of adherence, but the possibility that expecting pill-counts may act as a facilitator to adherence should not be discounted[429].

2.5.2.2 ***Employment***

When considering unemployment, out of 17 studies, three found it was associated with increased non-adherence[350;373;430] (two cross-sectional studies one longitudinal), while 14 found no statistically significant association[164;348;352;374;401;402;417;420;423;425-427;431;432]. Indeed, though no significant association was found, one of these 14 studies found some suggestion that the unemployed had *lower* odds of non-adherence[427].

In the only longitudinal study to find an association between employment and ART adherence, its participants had been recruited for a clinical trial due to prior evidence of non-adherence, therefore the results were unlikely to be generalisable[373]. Though the intervention, of an adherence form given to clinicians before routine appointments, was not found to affect adherence overall, it is possible that it had an impact on those who were employed more than those not employed.

2.5.2.3 ***Income/financial status***

Nine of 16 studies found that lower income/higher poverty was associated with greater ART non-adherence[347;349;375;410;420;426;432-434], whereas the remaining seven found no evidence of an association[348;352;353;401;416;417;421], and none found an association with *lower* non-adherence. A greater proportion of the studies which looked at a poverty related measure compared to absolute income found an association with non-adherence (5/7 vs. 4/11 where some studies considered both poverty and income outcomes).

In a study of individuals with low health literacy, although income and adherence were not associated (OR=0.99), poverty related stress was associated ART non-adherence (OR=1.37), a relationship which remained even in multivariate analyses (aOR=1.39)[420]. This implies that the negative material and psychosocial effects of very low income were associated with ART adherence even if income itself was not[435]. In studies where food insecurity or food and housing insecurity combined were considered, they were associated with non-adherence to ART[375;410;433]. The results of these studies provide further support that the physical effect of poverty is strongly linked to poor adherence.

2.5.2.4 ***Housing***

Poorer housing status was associated with greater non-adherence in nine studies[347;349;352;375;416;426;430;433;436], and no association in the remaining six studies[348;373;402;417;421;424].

In a cross-sectional study of data from an RCT of individuals who were homeless or at severe risk of homelessness (which had investigated the effects of providing rental

assistance) [424] and three other studies of RCT data, no association was found between housing status and self-reported adherence[417;424] or adherence measured by MEMS caps[373;421]. It is possible that there is a systematic difference between those who agree to participate in clinical trials and those who do not.

2.5.2.5 ***Health insurance***

Three of the four US-based studies of the association between insurance and non-adherence found either no insurance[424;426] or public insurance[351] was associated with greater non-adherence, but the remaining study found no association between adherence measured by MEMS caps and insurance[373].

In Estonia, heath care is financed by a mandatory health insurance system. In a cross-sectional study, uninsured individuals had 3.67 times the odds of non-adherence compared to insured individuals, however, there were only nine uninsured participants so there was a very wide confidence interval for this finding[427].

2.5.2.6 ***Neighbourhood SES***

Finally, two US-based studies considered neighbourhood-level SES, of which one found that higher neighbourhood poverty was associated with *lower* non-adherence to ART[416], and the other found no association[351]. In the former, the outcome studied was missed doses of ARVs for diversion-related reasons (selling or trading drugs), among a study population of active substance users[416]. However, in this same study, higher perceived neighbourhood disorder was strongly related to increased diversion-related non-adherence ($p<0.001$). This indicates that perhaps how individuals perceived the SES of their neighbourhood is more strongly related to their adherence to treatment than the actual status of the neighbourhood they lived in.

Table 2.9: Original research studies considering the association between ART non-adherence and socio-economic factors among people prescribed ART [a b]

Publication, Setting, date and study [c]	Sample size	Non-adherence outcome		Prevalence of SES groups		OR (95% CI) or Prevalence: Yes vs. No [d e]		Adjusted for in addition to gender & age
		Self-report	Definition (%)	Marker	Prevalence	Unadjusted	Adjusted	
Cross-sectional								
SHAS[436] US 2000-03	5,404 on ART	Yes	<100% in last 48 hrs (18%)	Homeless	5%	**2.17 (1.54, 3.13)**	**1.92 (1.18, 3.03)**	HIV acquisition risk, CD4, ethnicity, marital status, education, drug & alcohol use, employment, recent health status, income
SHCS[346] Switzerland 2003	3,607 on ART ≥6 mths	Yes	Miss≥1 dose in last 4 wks (31%)	Education length ≤9 yrs	26%	**1.25 (1.06, 1.49)**	1.11 (0.93, 1.33)	Ethnicity, living alone, IDU, dose frequency, psychiatric treatment, time on ART, previous regimens, lipodystrophy, current regimen
			Miss≥2 doses in last 4 wks (15%)	Education length ≤9 yrs		**1.37 (1.11, 1.69)**	1.15 (0.91, 1.45)	
			<95% in last 4 wks (7%)	Education length ≤9 yrs		**1.76 (1.33, 2.32)**	**1.42 (1.04, 1.94)**	
MMP[347] US 2007-08	3,307 on ART	Yes	<100% dose last 48 hrs (13%)	Education <high school	22%	NS	-	Ethnicity, other SES factors, depression, crack use, amphetamine use, binge drinking, time on ART, time since
				Homeless in last yr	7%	**1.71 (1.22, 2.41)**	NS	
				Public assistance in last yr	50%	**1.46 (1.19-1.79)**	**1.31 (1.05-1.65)**	

Publication, Setting, date and study [c]	Sample size	Non-adherence outcome		Prevalence of SES groups		OR (95% CI) or Prevalence: Yes vs. No [d e]		Adjusted for in addition to gender & age
		Self-report	Definition (%)	Marker	Prevalence	Unadjusted	Adjusted	
			<100% schedule last 48 hrs (27%)	Education <high school		**1.56 (1.32, 1.89)**	**1.28 (1.05, 1.56)**	diagnosis, dose frequency, knew VL, resistance discussed
				Homeless in last yr		**1.69 (1.28, 2.24)**	**1.43 (1.05, 1.95)**	
				Public assistance in last yr		**1.47 (1.26, 1.72)**	**1.35 (1.14, 1.60)**	
			<100% instruction last 48 hrs (30%)	Education <high school		NS	-	
				Homeless in last yr		**1.38 (0.98,1.94)**	NS	
				Public assistance in last yr		NS	-	
ANRS-VESPA[375] France 2003	1,809 on ART	Yes	Dose or schedule <100% in last 7 dys (27%)	Difficult household financial situation	MSM: 19% MSW: 33% Women: 33%	**50% v 40% p=0.03** **50% v 36% p<0.01** **52% v 41% p=0.03**	NS NS NS	[subsets of] migrant status, IDU, discrimination, time HIV-diagnosed, perceived adverse effects of ART, alcohol use, suicide attempts, other SES factors [h]
				Household food privation in last 4 wks	MSM: 6% MSW: 13% Women: 17%	52% v 41% p=0.13 **65% v 37% p<0.01** **56% v 43% p=0.04**	NS **2.35 (1.49, 3.71)** NS	
				Unsatisfactory housing conditions	MSM: 7% MSW: 18% Women: 20%	**58% v 40% p=0.01** **56% v 38% p<0.01** **56% v 42% p=0.02**	NS NS NS	
HIV Futures 6[423] Australia 2008-09	820 on ART	Yes	<100% in last 2 dys (39%)	Highest education level	n/k	p<0.2	p>0.1	Drug & alcohol use, smoking, health, STIs, mental health, disclosure, attitude,
				Employment		p>0.2		

Publication, Setting, date and study [c]	Sample size	Non-adherence outcome		Prevalence of SES groups		OR (95% CI) or Prevalence: Yes vs. No [d e]		Adjusted for in addition to gender & age
		Self-report	Definition (%)	Marker	Prevalence	Unadjusted	Adjusted	
				Income		p>0.2		support, ART frequency, discrimination, type of regimen, time on ART, symptoms, ADEs, latest CD4, urbanicity [h]
OCS[348] Canada 2007-09	779 on ART	Yes	<100% in last 4 dys (15%)	Education <high school	32%	**2.44 (1.38, 4.17)**	NS	HIV acquisition mode, ethnicity, region of birth, ART type, ART frequency, alcohol, depressive symptoms, general health, social support, stress, coping [h]
				Unemployed	57%	p=1.0	-	
				Household income <$40,000/yr	39%	p=0.2	-	
				Currently homeless	<1%	p=0.2	-	
Multi-centre RCT[424] US 2004-05	644 on ART	Yes	<100% in last 2 dys (22%)	Education <high school	n/k	24% v 21% p=0.6	1.20 (0.63, 2.29)	Ethnicity, problems accessing care, alcohol
				Homeless/unstable housing		21% v 31% p=0.3	-	
				Medically uninsured		34% v 20% p=0.06	-	
			<90% in last 7 dys (19%)	Education <high school		17% v 20% p=0.3	0.81 (0.41, 1.60)	Ethnicity, other SES factors, alcohol, drug use
				Homeless/unstable housing		17% v 20% p=0.74	-	
				Medically uninsured		26% v 16% p=0.2	**2.43 (1.04, 5.69)**	

Publication, Setting, date and study [c]	Sample size	Non-adherence outcome		Prevalence of SES groups		OR (95% CI) or Prevalence: Yes vs. No [d e]		Adjusted for in addition to gender & age
		Self-report	Definition (%)	Marker	Prevalence	Unadjusted	Adjusted	
Multicentre RCT: INSPIRE[417] US 2001-03	636 PWID, on ART	Yes	<90% on previous day (25%)	Education<high school	44%	**1.66 (1.16, 2.39)**	**1.57 (1.03, 2.41)**	Ethnicity, drug use behaviours, depression, attitudes to medication, baseline VL and CD4
				Unemployed	95%	NS	-	
				Annual income < $10,000	87%	NS	-	
				Homeless	28%	NS	-	
LISA[349] Canada 2007-10	556 on ART	No	Prescription refill <95% last yr (44%)	Education <high school	40%	31% of adherent vs. 52% non-adherent; **p<0.001**	NS	Ethnicity, other SES factors, incarceration, depressive symptoms, drug use, IDU, methadone treatment, ART frequency, medication memory aids, in assisted therapy program
				Annual income < $15,000/yr	59%	50% of adherent vs. 72% non-adherent; **p<0.001**	NS	
				Homeless/unstable housing	31%	25% of adherent vs. 61% non-adherent; **p<0.001**	**2.13 (1.39, 3.23)**	
SUN[350] US 2004-06	528 on ART	Yes	<100% in last 3 dys (16%)	Education <high school	22%	1.86 (0.98, 3.54)	1.39 (0.65, 2.95)	Ethnicity, time since HIV diagnosis, smoking, alcohol marijuana & cocaine use, mental & physical health, aerobic exercise, suicidal ideation, other SES factors [i]
				Unemployed	41%	**2.59 (1.53, 4.37)**	1.86 (0.99, 3.48)	
Single centre[410] US 2012	521 prescribed ART	Yes	<85% in last mth (25%)	Food insecurity in last mth	38%	**2.0 (1.33, 3.23)**	**2.0; p<0.01**	Housing, transportation, neighbourhood

Publication, Setting, date and study [c]	Sample size	Non-adherence outcome		Prevalence of SES groups		OR (95% CI) or Prevalence: Yes vs. No [d e]		Adjusted for in addition to gender & age
		Self-report	Definition (%)	Marker	Prevalence	Unadjusted	Adjusted	
								poverty, living in an area without a desert
Single centre[433] US 2010-2012	503 on ART active substance users	Yes	<95% in last wk (46%)	Combined food and housing insecurity	43%	**53% v 41% p<0.01**	**Standardised β=-0.95 (-0.122, -0.002) p=0.044**	Depression, anxiety, trauma, dependence, treatment access, mths in care, ARV diversion [f j]
Single centre[416] US 2010-12	503 on ART active substance users	Yes	<100% in last wk diversion-related [f] (30%)	Education <high school	44%	**1.52 (1.03, 2.22)**	-	ethnicity, income, substance dependence, homelessness, individuals selling/trading ARVs in personal network
				Income < $1,000/mth	81%	0.96 (0.59, 1.56)	-	
				Housing in past 90 dys:				
				In public housing	*23%*	-	-	
				Stay with friend/relative	*13%*	***2.41 (1.33, 4.39)***	-	
				Homeless	*39%*	***1.97 (1.34, 2.90)***	***1.72 (1.13, 2.63)***	
				Perceived disorder in neighbourhood		**1.03 (1.01, 1.05)**	1.01 (0.99, 1.03)	
				Neighbourhood % below poverty level		**0.98 (0.96, 0.99)**	-	
5 centres[374] UK 2005-06	502 on ART	Yes	<100% in last wk dose schedule and instruction (58%)	Education <university	54%	n/k	**0.54 p=0.03**	
				Non-employed	47%		NS	
5 centres[164] UK 2005-06	486 on ART	Yes	<100% dose schedule and instruction in last wk (51%)	Education <university	53%	57% v 58% p=0.73	n/k	
				Non-employed	42%	55% v 58% p=0.63		

Publication, Setting, date and study [c]	Sample size	Non-adherence outcome		Prevalence of SES groups		OR (95% CI) or Prevalence: Yes vs. No [d e]		Adjusted for in addition to gender & age
		Self-report	Definition (%)	Marker	Prevalence	Unadjusted	Adjusted	
			<100% dose in last wk (20%)	Education <university Non-employed		22% v 21% p=0.84 21% v 21% p=0.84		
			≥2 doses missed in last wk (7%)	Education <university Non-employed		12% v 8% p=0.24 10% v 10% p=0.52		
CHS HIV Wave 4 Patient study[431] US 2007	461 on ART	Yes	<100% average wk (46%)	non-employed	56%	Employed: 44% adherent vs. 44% non-adherent p=0.88	1.12 (0.69, 1.83)	Ethnicity, insurance, cost manageability, drug use, ART satisfaction, daily pill count, comorbidities
Single centre[402] US 2007	370 on ART	Yes	<95% in last 4 dys (25%)	Education<high school Unemployed Homeless	49% 59% 8%	**33% v 23% p<0.05** NS NS	n/k	
RCT[425] US 2007-09	326 on ART	Yes	<100% in last 4 dys (40%)	Education <high school **Employment:** *Employed* *Non-employed (health related)* *Non-employed (non-health related)*	41% *21%* *65%* *14%*	0.95 (0.79, 1.16) *1.00* *1.01 (0.78, 1.29)* *1.06 (0.88, 1.27)*	n/k	
Multi-centre RCT[422] US 2004-09	192 previously ART-naïve/ART	No	MEMS over 7 dys	Education <high school	22%	r=0.092	No causal pathways between education, coping and adherence	Coping

Publication, Setting, date and study [c]	Sample size	Non-adherence outcome		Prevalence of SES groups		OR (95% CI) or Prevalence: Yes vs. No [d e]		Adjusted for in addition to gender & age
		Self-report	Definition (%)	Marker	Prevalence	Unadjusted	Adjusted	
	switch/ non-adherent							
Project Gold[418] US 2010-11	180 On ART MSM >50 yrs	Yes	<100% dose in last 4 dys (20%) <100% schedule in last 4 dys (48%) <100% instruction in last 4 dys (24%) <100% dose last weekend (18%)	Education <university	67%	1.14 (0.52, 2.50) 1.75 (0.93, 3.33) 2.33 (0.98, 5.55) 1.15 (0.51, 2.63)	0.99 (0.44, 2.22) 1.61 (0.82, 3.13) 1.85 (0.75, 4.55) 0.97 (0.41, 2.27)	HIV-related stigma [h] Depression, HIV-related stigma, sexual compulsivity [h] Depression, HIV-related stigma, body distress, sexual compulsivity [h] sexual compulsivity [h]
5 centres[428] UK 2005-06	170 on ART heterosexual	Yes	<100% dose schedule & instruction in last wk (56%)	Education <university	Men: 61% Women: 67%	**3.18 (1.02, 9.86)** **0.25 (0.09, 0.66)**	2.64 (0.63, 10.9) **0.26 (0.09, 0.76)**	Ethnicity, UK birth, disclosure, symptoms [h]
Single centre[427] Estonia 2010	144 on ART	Yes	<100% last 3 dys (12%)	Length education<9 yrs Unemployed (receiving benefits) Medically uninsured	30% 73%	0.43 (0.08, 1.67) 0.55 (0.14, 2.16) 3.67 (0.73, 15.46)	0.36 (0.08, 1.23) 0.50 (0.14, 1.91) **4.41 (1.03, 17.2)**	Insurance, SR health [j]
Single centre[430] Spain	143 on ART	Both	Self-report or prescription refill <100% (33%)	Employment; Housing	n/k	n/k	Both **independent predictors** of good adherence	

Publication, Setting, date and study [c]	Sample size	Non-adherence outcome		Prevalence of SES groups		OR (95% CI) or Prevalence: Yes vs. No [d e]		Adjusted for in addition to gender & age
		Self-report	Definition (%)	Marker	Prevalence	Unadjusted	Adjusted	
Single centre[426] US 2006	132 on ART	Both	Self-report, detectable VL without resistance, lack of prescription refill or clinician report <100% last wk (26%)	Education<high school	28%	33% of adherent vs. 15% non-adherent p=0.09	n/k	
				Unemployed	55%	54% of adherent vs. 64% non-adherent p=0.14		
				Living in someone else's house	31%	26% of adherent vs. 53% non-adherent **p=0.01**		
				Annual income≤$10,000	42%	40% of adherent vs. 61% non-adherent **p=0.05**		
				Medically Uninsured	13%	10% of adherent vs. 25% non-adherent **p=0.02**		
Single centre[432] US	116 on ART	Yes	<95% last mth (39%)	Unemployed	62%	Non-employed: 59% of adherent vs. 67% non-adherent	n/k	
				Annual income <$10,000	63%	<$850/mth income: 52% of adherent vs. 62% non-adherent		
Longitudinal								

Publication, Setting, date and study [c]	Sample size	Non-adherence outcome		Prevalence of SES groups		OR (95% CI) or Prevalence: Yes vs. No [d e]		Adjusted for in addition to gender & age
		Self-report	Definition (%)	Marker	Prevalence	Unadjusted	Adjusted	
SHCS[354] Switzerland 2003-09	6,709 on ART	Yes	100% to <100% last 4 wks 2 measurements 6 mths apart (17%)	"Basic" education	27%	n/k	**1.16 (1.03, 1.31)**	Ethnicity, living alone, ended stable partnership, started IDU, started drug maintenance program, alcohol, smoking, risky sex, psychiatric treatment, prison release, hospitalised, time living with ART, co-medication, ART change, regimen frequency change, time on ART, lipodystrophy, physician change, adherence at first visit
			<100% to 100% last 4 wks 2 measurements 6 mths apart (18%)	"Basic" education		n/k	**0.82 (0.68, 0.99)**	
KPNC[351] US 1996-2005	4,686 initiating ART	No	Mean prescription refill mean over 2 yrs since ART initiation	Public insurance	11%	n/k	**−4.8% (−7.7, −2.0) p<0.001**	HIV acquisition risk, ethnicity, yr ART start, baseline VL and CD4, ART experience, ART regimen, HCV, Depression, comorbidities, other SES factors
				Live in area with >25% individuals<high school education	23%		-1.3% (−3.4, 0.8) p=0.21	
				Live in area with>20% below poverty line	16%		-0.8% (−3.2, 1.6) p=0.52	

Publication, Setting, date and study [c]	Sample size	Non-adherence outcome		Prevalence of SES groups		OR (95% CI) or Prevalence: Yes vs. No [d e]		Adjusted for in addition to gender & age
		Self-report	Definition (%)	Marker	Prevalence	Unadjusted	Adjusted	
MACH14[353] US 1997-2009	1,809 on ART	No	MEMS mean over 4-wk periods	Education<high school Annual household income<$10,000`	23% 59%	n/k	**1.24 (1.06, 1.44)** 1.06 (0.93, 1.20)	Ethnicity, site, other SES factor, substance use, depression
MACS[434] US 2003-09	712 on ART MSM	Yes	Score from 1-4 (1=high and 4 =low) since last visit	Annual income<$20,000	19%	n/k	<$20,000: **mean=1.81** >$20,000: **mean=1.73** p<0.0001	Ethnicity, sex with women, recent seroconversion [h]
Multi-centre[401] US 2013-14	418 on ART food insecure	No	Unannounced telephone pill count <85% measured 3 times in 6 wks (43%)	Number yrs of education; Non-employed Annual income<$10,000 Number food insecurity indicators	 87% 68%	n/k	0.97 (0.86, 1.10) /additional yr 1.05 (0.84, 1.32) 1.19 (0.88, 1.62) 1.02 (0.91, 1.16) /additional indicator	Yrs HIV diagnosed, alcohol, drug use, side-effects, medication necessity and concern beliefs, ART regimen food requirements, other SES factors [j]
Project MOTIV8 multi-centre RCT[421] US 2004-09	204 ART-naïve/ adherence problems/	No	MEMS <90% over 30 dys before yr 1 visit (41%)	Education<high school Include≤$1,000/mth Insecure housing	23% 63% 35%	46% v 33% p=0.11 45% v 35% p=0.19 45% v 39% p=0.45	n/k	

Publication, Setting, date and study [c]	Sample size	Non-adherence outcome		Prevalence of SES groups		OR (95% CI) or Prevalence: Yes vs. No [d e]		Adjusted for in addition to gender & age
		Self-report	Definition (%)	Marker	Prevalence	Unadjusted	Adjusted	
	switching ART		MEMS <90% over 30 dys before yr 2 visit (44%)	Education<high school Include≤$1,000/mth Insecure housing		53% v 37% p=0.16 48% v 38% p=0.21 50% v 41% p=0.30		
Multi-centre[420] US 2008-09	188 on ART with poor health literacy	No	Unannounced telephone pill-count <85% over a mth (67%)	Yrs of education Non-employed Annual Income High poverty-related stress	 96% 70% n/k	1.00 (0.85, 1.18) /yr fewer 1.15 (0.84, 1.59) 0.99 (0.64, 1.52) **1.37 (1.16, 1.61)**	 **1.39 (1.12, 1.69)**	Social stressors, stress severity, depression, internalised stigma, drug use [j]
Multi-centre[419] US	145 on ART	No	Unannounced telephone pill-count <85% over a mth (75%)	Yrs of education	n/k	n/k	1.20 (0.95, 1.49) /yr fewer	Yrs HIV diagnosed, symptoms, depression, stigma, social support, alcohol, literacy [h]
Two centre RCT[373] US 2002-05	137 on ART with detectable VL	No	MEMS change in 30 dys following each study visit	Education<primary level Non-employed Homeless	5% 66% 6%	NS Difference=-11.5 p<0.05 NS	- Difference =-7.8 p>0.05 -	HIV acquisition risk, ethnicity, education, marital status, ART type, physical & mental scores, depressive symptoms, stage of change [g]

Publication, Setting, date and study [c]	Sample size	Non-adherence outcome		Prevalence of SES groups		OR (95% CI) or Prevalence: Yes vs. No [d e]		Adjusted for in addition to gender & age
		Self-report	Definition (%)	Marker	Prevalence	Unadjusted	Adjusted	
HERO[352] US 1998-2001	113 prescribed ART current/ former opioid users	No	MEMS median over study period	Unemployed Receive public assistance No long term housing	86% 9% 55%	NS NS **42% v75% p=.003**	n/k	

Red= higher SES group were less likely to be non-adherent to ART than lower SES group; Green= higher SES group were more likely to be non-adherent to ART than lower SES group; **bold**= estimates with associated p-values of <0.05.

[a] Studies recruited not entirely before 2001, with sample size >100; [b] studies ordered by study size within each category (cross-sectional and longitudinal); [c] refer to list of relevant study acronyms on pages 10-11 for full study names; [d] estimates are standardised such that the lower SES group is compared with the higher one; [e] standardised such that non-adherence is the outcome; f ARV diversion is the selling or trading of ARVs; [g] stage of change= model for changing behaviour; [h] not adjusted for gender; [i] not adjusted for age; [j] not adjusted for gender or age; SR= self-reported; MEMS=Medical Event Monitoring System; IDU= injection drug use; HCV=Hepatitis C virus; RCT= Randomised Controlled Trial; ADE=AIDS Defining Event; NS=not significant association but estimates not given; n/k=not known; N/A=not applicable; yr/s=year/s; mth/s=month/s; wk/s=weeks; CI=Confidence Interval; OR=Odds Ratio.

2.5.3 **Discussion - Association between SES and ART-related outcomes**

This review provides substantial evidence of an adverse effect of lower SES on virological and immunological outcomes among individuals prescribed ART. In particular, 12 of the 17 (71%) studies across various high-income settings have demonstrated a negative effect of lower SES on VL outcomes. In some studies this effect was strong[342;359;402;403;405], suggesting lower SES may be one of the most important predictors of treatment success. Few of the studies reviewed identified that those in lower socio-economic groups had better treatment outcomes.

There exists considerable evidence of socio-economic disparities in prognosis[318;437-440] and adherence to treatment[441-443] for a number of other chronic conditions. The finding of the present chapter, that HIV-diagnosed people with lower SES were often more likely to have poorer treatment outcomes, was consistent with similar results for other conditions, and adds to the existing evidence of the adverse impact of social disadvantage on health outcomes[444-447].

Each individual socio-economic factor portrays a different aspect of SES. Identification of the most important measure may provide some insight into potential mechanisms of action[448]. However, there was considerable multi-collinearity between the indicators which may make simultaneous investigation problematic[449]. It can be difficult to interpret results from multivariable models that include more than one socio-economic factor[401;402;410], particularly when the unadjusted associations between these factors and ART response are not presented[401].

Few of the studies identified as assessing the association between SES and VL outcome were in European settings (only six of 17); however, they seemed equally as likely to find an adverse effect of lower SES as studies in the US, a setting without free access to healthcare. This indicated that the main factors for this specific question on ART response go beyond those related to healthcare system. In a review of socio-economic inequalities in mortality and morbidity in 22 European countries, there was no evidence of systematically smaller socio-economic inequalities in health in Northern Europe compared to other areas of Europe, despite increased welfare support and lower prevalence of poverty[286]. This adds weight to the idea that socio-economic disparities in health are not solely a result of inability to pay for treatment. Therefore, greater understanding of the effect of socio-economic factors on HIV treatment outcomes in a setting with universal healthcare also has implications for settings without this.

The findings of this review have a number of potential caveats. Previously, substantial differences in the magnitude of socio-economic inequalities in health across European settings have been found[286]. Thus, the presence or magnitude of the association between SES and ART outcomes cannot be assumed generalisable across countries and healthcare settings. Due to differing definitions of SES, ART response outcomes and non-adherence across studies it is difficult to directly compare associations. Furthermore, the extent of the variation in social circumstances in the study sample may influence the magnitude of observed associations. Confounding could also be an issue, as several of the reviewed studies were not designed to specifically examine the effects of socio-economic factors themselves; this was particularly prevalent among the studies which looked at adherence outcomes. Some studies reported on the effects of SES among generally low SES populations, for example among food insecure individuals, however, a number of studies both in low SES populations and in more varied SES populations found consistent results. All studies that were reviewed, except one[406], excluded individuals with missing values from VL or CD4 endpoints or censored follow-up at the last available measurement. If lower SES is associated with poorer retention in care[450;451], then these studies may underestimate socio-economic effects.

Of the six European studies of SES and VL identified, three considered education as the sole SES indicator, one solely considered employment status, and one only considered neighbourhood-level SES. Thus only one European study considered multiple markers of SES[359]. Education may be problematic as a marker of SES as it does not necessarily capture current resources or living conditions (for example SES of migrants in the country of migration). Likewise, neighbourhood-level SES is not necessarily a reliable marker of an individual's situation. At present, there is little information from studies in Europe on the effect of poverty and adverse social circumstances on HIV treatment outcomes. Other gaps in the literature include studies that test specific hypotheses about the mechanisms through which SES affects health outcomes and adherence. Moreover, quantitative and qualitative research is needed to better understand these precise mechanisms and to inform intervention approaches. A review of the literature on the effect of SES on other points in the care continuum would also be valuable. My review highlights the need for routine assessment and documentation of socio-economic factors in the clinic setting, to identify, and in turn give support to, those at greater risk of ART non-adherence and poorer ART response.

This literature review adds evidence of socio-economic disparities in HIV treatment outcomes to the disparities already identified by gender/sexual orientation.

Furthermore, it suggests gaps in the current literature that require analysis to gain understanding of the associations between SES and ART response.

2.6 **Review of potential mediators for any gender/sexual orientation and SES differences in HIV-treatment outcomes**

In the literature reviews in Sections 2.4 and 2.5, associations of HIV treatment response with gender/sexual orientation and socio-economic disadvantage were identified respectively. Here, I will summarise studies that have included both types of factors in multivariable models to assess the extent to which any associations are attenuated (Section 2.6.1). Then I shall consider other proposed mechanisms through which gender/sexual orientation and SES may affect ART outcomes (Section 2.6.2).

The method of identifying potential mediating factors by looking at the effect of adjustment for these factors has its limitations. It is difficult to gain an understanding of which factors attenuate associations between the outcome and explanatory variable of interest when multiple covariates are adjusted for simultaneously. Additionally, if unadjusted analyses are not presented, then it is not possible to investigate the mediating role of the factors included in adjusted analyses[343;364;401]. Adding covariates to the model sequentially would allow analysis of the extent to which these factors account for any associations.

2.6.1 **The interaction between gender/sexual orientation and SES**

The prevalence of socio-economic disadvantage differed by gender/sexual orientation groups in several European studies[357;364;375]. In the French ANRS study, heterosexual migrants were more likely to have precarious housing conditions, to report financial difficulties and food privation, to report social isolation and to be single parents than MSM[364]. Likewise, in the SHCS only 13% and 40% of the single heterosexual migrants and older MSW, respectively, had paid work as their main source of income, compared to 90% of MSM[357]. Therefore, virological response differences between these groups could partially result from SES inequalities. However, these studies did not adjust their measures of the association between gender/sexual orientation and virological response for these socio-economic factors so it was not possible to assess their interaction.

Gender/sexual orientation and socio-economic factors were jointly considered in four studies. Unadjusted analyses of the SHCS[126] found women had lower odds of VL suppression compared to MSW and a higher proportion in the lowest education category. Adjustment for educational attainment, among other factors, only reduced

the OR of virological suppression by 4%, although this no longer reached statistical significance (p=0.13). In contrast, the CoRIS[405] study focused on SES. The ORs of VL suppression among individuals in the low education group at six and 12 months of ART were attenuated by 18% and 55%, respectively after adjustment for gender/sexual orientation. In the HOPS[363] and ANRS[359] studies, univariable associations of both gender/sexual orientation and socio-economic factors with virological suppression were attenuated towards one in multivariable analyses.

There was also some evidence of the ability of SES to explain gender disparities in other areas of health such as mental health[452], and that women's greater exposure to stress and life events[453] or lower incomes[454] were substantial contributors to poorer health among women.

It is difficult to make any firm conclusions about whether SES acts as a mediator for gender/sexual orientation on response to ART since it was not the focus of any study identified by my literature reviews and only the four described above had any information I could use to address this question.

2.6.2 **Potential mediators of the association of gender/sexual orientation or SES with virological and immunological outcomes**

2.6.2.1 ***ART non-adherence***

Until this point, ART non-adherence has been considered as an outcome. However, adherence to ART is key in achieving the outcome of virological suppression[170;455]. Furthermore, there was some evidence from my literature reviews of differences in non-adherence by gender/sexual orientation and SES. Thus it is likely that adherence is on the causal pathway between SES/gender/sexual orientation and HIV treatment outcomes[199;456].

Only two studies of the association between gender/sexual orientation and treatment outcomes, both from the ANRS cohort, looked at the effect of adjusting for adherence. Dray Spira et al. found that, despite poorer adherence to ART among heterosexual migrants, adjustment for adherence, among other factors, did not account for VL or CD4 count outcome differences between heterosexual migrants and MSM[364]. On the other hand, D'Almeida et al. found that associations were attenuated, but did not completely disappear. However, many other factors had also been adjusted for, including SES[359].

Although the RFHCS did not measure ART adherence, they considered rates of complete ART discontinuation[362]. A model that did not censor follow-up at ART discontinuation, found women had 41% higher hazard of virological rebound compared

to MSW. In an alternative analysis that did censor follow-up at ART discontinuation, this was attenuated to 30%. Thus, higher rates of complete ART discontinuation among women (15% vs. 9% among MSW in the first 12 months of ART) may explain at least some of the observed VL outcome differences.

Four studies examined the extent to which non-adherence explained the associations between SES and ART response. In the VACS, food insecurity was associated with 37% higher odds of virological non-suppression in analyses adjusted for demographic, lifestyle and other SES factors[400]. Further adjustment for self-reported adherence attenuated associations to some extent, however, food insecure individuals still had 32% greater odds of non-suppression. In the ACCESS study of PWID, homelessness was associated with 67% higher adjusted rates of VL non-suppression compared to housed individuals in a model adjusted for age, recent incarceration, year of ART initiation and baseline VL[404]. However, homelessness was no longer associated with VL non-suppression after additional adjustment for ART adherence (attenuated by an additional 19%).

The remaining two studies adjusted for adherence in the same stage as other factors (including baseline HIV factors such as VL and ART regimen, demographic factors and other socio-economic factors) and so it was not possible to isolate the effect of adjustment for non-adherence. Nonetheless, in a single-centre US-based study[403], and the ANRS study[359], there were still substantially lower odds of virological suppression for individuals with poorer education and/or employment status after adjustment. In contrast, in the latter study, associations between deprivation and lower odds of sustained VL suppression were attenuated to one in multivariable analyses.

2.6.2.2 ***Calendar Time***

Over time, inequalities in treatment response by gender or SES may be reduced by improvements in the efficacy and tolerability of ARVs, earlier HIV diagnosis, and improved knowledge of the importance of adherence. Only two of the identified studies, both from the RFHCS, considered changes over time. Lampe et al. showed that the prevalence of VL >50 copies/mL decreased between 1999 and 2004, but the relative differences between gender/sexual orientation groups remained of the same magnitude across all time periods[365]. An earlier study found more rapid reductions over time among MSM compared to MSW and women in the risk of VL >200 copies/mL after six months of ART[457]. Follow-up in both of these studies ended over ten years ago, and therefore it would be of interest to see whether differences over time are narrowing in more recent years.

2.6.2.3 *Delayed diagnosis and initiation of treatment*

Late diagnosis and late initiation of treatment are often difficult to disentangle when looking at their effect on treatment response, since individuals diagnosed with a low CD4 count are inevitably going to initiate ART late. Late diagnosis is considered here in the context of an explanatory factor for ART response. Differences in late diagnosis as an outcome by gender/sexual orientation and SES will be fully discussed in Chapter 9.

Being diagnosed and/or starting treatment with a low CD4 count has been shown to have a negative impact on HIV progression, particularly immunological response to ART[135;458-462]. Prior studies have shown that women may delay ART initiation more frequently than men[463]. Three studies (two French and one Swiss) found that although MSM had a higher median CD4 count at ART initiation than MSW and women, adjustment for this (amongst other factors) did not account for gender/sexual orientation differences in virological or immunological response[357;361;364]. An American study of individuals initiating ART within six months of eligibility (CD4 count <350 cells/μL or AIDS-defining condition) found no difference in time to virological suppression between women and MSM[360]. This could suggest that associations were not present among individuals initiating ART with a higher CD4 count. However, the study only provided estimates adjusted for demographic and eligibility-related factors, so one or more of these might have already accounted for any potential differences.

Socio-economically disadvantaged individuals may initiate treatment at a later stage for a range of reasons including competing priorities, lower health literacy and less knowledge about ART. Neighbourhood unemployment levels were associated with delayed access to treatment in a study of HIV-related deaths in Canada[464]. However, this study was not in the context of the impact of late treatment initiation on ART responses. The SHCS[126] and CoRIS studies[405] found that adjustment for CD4 count and VL at ART initiation, along with demographic factors, attenuated the effect size of associations between virological response and educational attainment.

2.6.2.4 *ART regimen*

There is a wide choice of efficacious ART regimens in high-income settings in the modern ART era. Despite this, residual differences in efficacy[465-469], differential adherence patterns[468;470;471] related to side-effects[472;473], food requirements, dietary restrictions, pill burden, and dose frequency could affect virological response according to the specific ART regimen used. Thus, ART regimen could act as a confounder if there are also differences in prescribing patterns between gender/sexual orientation or socio-economic groups.

Different ART regimens require differing levels of adherence in order to maintain virological suppression[474;475]. In particular, NNRTI-based regimens require lower levels of adherence than un-boosted PI-based regimens[384], but greater levels of adherence than the forgiving RTV-boosted PI-based regimens[192]. There is also evidence of higher odds of women choosing PI-based regimens over NNRTI-based (OR=1.25)[476], likely due to EFV being contra-indicated during pregnancy. Thus, women may require lower levels of adherence to ART to maintain virological suppression. It will be interesting to monitor this in future years as use of other ARVs, particularly integrase inhibitors, increases. Even when men and women were prescribed the same regimen, previous studies have shown that prevalence of side effects can differ[477-479]. This may be related to women on average having a lower weight, but receiving the same dose as men. So even if prescribed the same regimen women may have greater difficulties in adhering to treatment than men.

Some studies have indicated that food requirements for taking ART may have been a barrier to adherence to treatment for socio-economically disadvantaged individuals[401]. Thus, through adherence, certain ART regimens may be detrimental to treatment for these groups in particular.

2.6.2.5 ***Healthcare***

In general, women are more likely than men to access healthcare in high income settings[480;481]. Women may make greater use of healthcare services because they have a greater number of chronic conditions, burden of symptoms or need for treatment[480]. Alternatively, there is evidence of differences in health seeking behaviour[235;279;482]. Women and men have different healthcare needs, for example attendance at clinics for contraception, pregnancy and menopause may mean that women attend healthcare settings more frequently and therefore may have better retention in HIV care if co-located. However despite this, in HIV[483] and several other health areas[481;484;485], there is evidence that women may not have had access to or the same quality of treatment as men.

In settings without universal free access to healthcare, an individual's ability to freely access HIV facilities is likely to provide an advantage in terms of maintaining engagement with medical care and achieving a good treatment response, particularly for individuals with lower incomes[486]. In all settings, inequalities in availability of resources, such as transport, may lead to inequalities in access of optimal healthcare resources[487]. Studies have also shown that it is possible that healthcare provider bias will affect the care that socio-economically disadvantaged individuals receive in various areas of health[488-490].

2.6.2.6 ***Mental health and lifestyle factors***

Depression and substance dependence are associated with poorer response to ART[402;491]. The effect of mental health, and drug or alcohol use on VL outcome would likely act at least partially through poorer adherence[492-494], although studies have also identified a direct biological effect of depression on immune response[495].

A meta-analysis of 10 studies concluded that development of depression was not associated with sexual orientation among PLWH[496]. However, several studies have reported greater levels of depressive symptoms among women compared to men in the HIV-positive population[497-499]. In a US-based study of RCT data, a model adjusted for depressive symptoms, among other factors, attenuated the difference in adherence between MSM and women[373]. Amongst women, particularly those of black African ethnicity, depressive symptoms were strongly associated with greater rate of virological failure[408]. Interventions such as mental health care may improve adherence to ART among women, while treatment for illegal drug use has been positively associated with adherence in men[500].

Substance use and mental health problems are generally more prevalent among socio-economically disadvantaged individuals[501-504]. In the UK-based Antiretrovirals, Sexual Transmission Risk and Attitudes (ASTRA) study, depressive symptoms were associated with poorer virological response to treatment and strongly with adverse socio-economic circumstances[505]. Three studies found no association between socio-economic deprivation and virological response to ART in analyses adjusted for factors including substance use and/or depression[343;359;401].

2.6.2.7 ***Ethnicity and migration***

Although not mediating factors for the association between gender/sexual orientation and virological response to ART, ethnicity and migration are intrinsically linked to gender/sexual orientation among PLWH. Three European, longitudinal studies previously identified considered an explanatory variable that combined gender/sexual orientation with other demographic factors[357;364;365]. They identified differences in virological response between MSM (of unspecified ethnicity/migrant status) and heterosexual non-migrant groups, but not to the same extent as those found between MSM and heterosexual migrants[357;364;365]. These results suggest differences in virological responses by migrant status may drive at least some of the differences between heterosexual and MSM groups.

Chapter 3 Thesis rationale, aims, and objectives

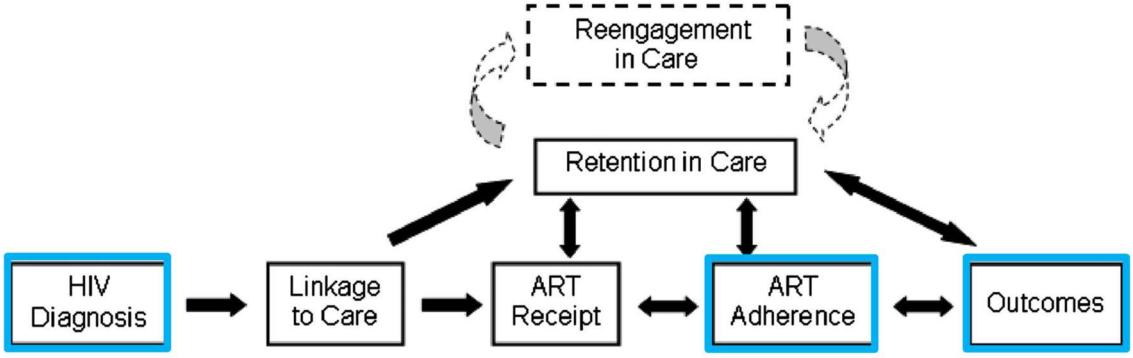
3.1 Rationale

Saunders et al. in 2013 considered gender/sexual orientation differences in response to first-line treatment among HIV-positive individuals attending the Royal Free Hospital, London, UK[362]. The authors concluded that worse virological outcomes for women persist and suggested that a potential factor influencing this difference may be socio-economic status, although no data were available to test this hypothesis. As a result of this study, the motivation for my thesis was to assess differences in virological response to cART between MSM, non-MSM men and women in recent years, and to investigate whether socio-economic factors may contribute to such differences.

In the era of effective ART, which nonetheless requires life-long adherence to treatment[162], the literature reviews conducted in Chapter 2 highlighted poorer HIV treatment outcomes among MSW and women compared to MSM, and among individuals with socio-economic disadvantage. With respect to SES, few studies have been performed in settings with universal free access to care (none in the UK), and these generally only consider education status. In the HIV setting, gender/sexual orientation and SES may be fundamentally linked, but further study is required into their joint effects. The literature reviews from the previous chapter identified several research gaps including: (i) changes over calendar time in virological and CD4 count response to ART by gender/sexual orientation; (ii) differences in VL and CD4 count response to ART by SES in a UK setting; and (iii) the mediating effect of SES on differences in ART response by gender/sexual orientation.

It is important to study socio-demographic variation at specific points in the continuum of care, and to assess whether such disparities have persisted in more recent years. My thesis focuses on the three specific areas of the care continuum outlined in blue in Figure 3.1[506]. Primarily the focus will be on treatment adherence and response to treatment for the reasons discussed above, but I will also consider HIV diagnosis. Individuals in high-risk groups for acquiring HIV, such as MSM and PWID, may be less likely to be diagnosed late than individuals not in high-risk groups since they are perceived by themselves and by health-care professionals as in greater need for frequent HIV testing. Therefore, it is of interest to assess whether there are gender/ sexual orientation disparities in access to a timely HIV diagnosis and what the reasons for any differences may be. A literature review for studies considering late diagnosis and gender/sexual orientation is included in Chapter 9.

Figure 3.1: Process for treatment success with steps from the treatment cascade



3.2 **Aims and objectives**

In this thesis there were four main aims:

1. To build an understanding of the existence of inequalities in virological response to ART by gender/sexual orientation and SES in the UK;
2. To evaluate whether these gender/sexual orientation differences have narrowed in more recent years;
3. To observe whether SES disparities contribute to any gender/sexual orientation differences in virological response;
4. To identify the relationship of gender/sexual orientation and SES with late HIV diagnosis in the UK.

In order to address these aims, the objectives of this thesis were:

- To assess the trends over calendar time in VL and CD4 count by gender/sexual orientation among a whole UK-clinic population (Chapter 5);
- To assess the trends over calendar time in initial virological response to treatment by gender/sexual orientation (Chapter 6);
- To evaluate the association between socio-economic disadvantage, by several markers, and virological response to ART (Chapter 7);
- To evaluate the ability of socio-economic factors to attenuate associations between gender/sexual orientation and virological response to ART (Chapter 8);
- To assess the differences in late diagnosis by gender/sexual orientation and SES (Chapter 9 - the literature review for this is included in the chapter itself).

3.3 **My contribution**

I played a major part in developing all of the research questions for this thesis in discussion with my PhD supervisors, and I decided upon the specific aims of each chapter that were to be addressed. I conducted all of the literature reviews that were presented in Chapter 2. For the data collected from the patient registration forms (used in Chapter 9), I was the first to analyse data from this source, and so cleaned the data and decided upon the best way to classify variables. I planned and conducted the analyses, including deriving additional required variables from those that existed currently in the data sets. I wrote programs to perform multiple imputation. I prepared all of the tables and figures presented in the results chapters of this thesis. I wrote up the results of each of the five analysis chapters and interpreted the results accordingly. I also considered and summarised the strengths and limitations of my work and the clinical implications.

Chapter 4 Data collection and methods

4.1 Introduction

This chapter will describe the data sources and statistical methods used throughout this thesis. The analyses presented in this thesis are based on two UK-based observational studies: The Royal Free HIV Cohort Study (RFHCS) and the Antiretrovirals, Sexual Transmission Risk and Attitudes (ASTRA) questionnaire study. Information on these data sources will include details of the study design; a summary of the study population; a description of the data collection methods and procedures; and definitions of the variables included. In terms of the statistical methods used, this chapter will include background information on each method and considerations that need to be made when using these methods.

4.2 The Royal Free HIV Cohort Study

4.2.1 Source of the data

The Ian Charleston Day Centre (ICDC) is an HIV-outpatient clinic at the Royal Free Hospital, London, UK. Professor Margaret Johnson helped to set up the ICDC in 1989, which was the first open access HIV clinic in the UK[507]. The ICDC provides a National Health Service (NHS) trust-funded multidisciplinary service for people living with HIV (PLWH). Currently there are over 3000 PLWH attending the ICDC.

At the ICDC there are specific services for women in the form of a weekly Women's HIV clinic. This involves a number of HIV clinicians predominantly seeing women on Wednesdays, and the following services are also provided on a Wednesday: Gynaecology advice available weekly, including everything from smears, contraception advice and HRT; sexual health screening, a monthly colposcopy service; antenatal clinics/MDTs and breast awareness clinics[508]. Immediate peer support does not coincide but there is psychology support available and access on site peer support the following day or referrals to peer support externally.

4.2.2 Study design

The RFHCS is an observational database based on data collected at the ICDC on HIV-diagnosed individuals attending the clinic. Although the clinic opened in 1989, the RFHCS was not set up until 1994. For the period 1991 to 1994, a retrospective chart review was conducted by Professor Amanda Mocroft to extract information on all individuals seen in that time. From 1994 to the present day, data have been collected

prospectively on all individuals that have ever attended the clinic with a full notes review conducted annually. The database is used to address questions related to treatment, prognosis and clinical management of HIV in the UK. In this thesis, the dataset used provides information up until March 2015 (the administrative censoring date).

4.2.3 **Study population**

Six thousand four hundred and twenty-three individuals have met the inclusion criteria for the RFHCS and are currently included in the database. Inclusion criteria are being HIV positive, having attended the ICDC on at least one occasion as an outpatient, and aged ≥16 years old at the first visit. Individuals were excluded if they acquired HIV through vertical transmission or through receipt of blood products, since these are quite distinct populations compared to individuals with HIV transmission through other routes, specifically in terms of: a greater number of years since HIV infection, likely limited therapeutic options early in infection[509], greater likelihood of being ARV-experienced at cART initiation, and a greater risk of co-infection with Hepatitis C (HCV) in the case of individuals infected through blood products[510].

4.2.4 **Data collection**

4.2.4.1 ***Patient registration forms***

At an individual's first visit to the ICDC, a full clinical and social history is taken. This is collected on a patient registration report form (Appendix I.), which is manually completed by clinic staff for the purposes of routine care, and subsequently digitised and included in the RFHCS database. The latest version of the registration form was introduced in April 2011 and differed from previous versions of the form, in that it additionally included data on socio-economic factors, and encounters with healthcare providers in the year prior to HIV diagnosis, information that my analyses in Chapter 9 of this thesis are the first to have used. A summary of the data collected by the patient registration form that are relevant to this thesis are shown in Table 4.1.

Table 4.1: Data fields collected on the patient registration form

Variable category	Variable
Identifier	Hospital number
Visit details	Date of visit
Demographic factors	Date of birth
	Sex
	Ethnicity
Clinical details	Most recent CD4 count
	Most recent VL measurement
Presentation details	Ever negative HIV antibody test
	Date of last negative antibody test
	Date of first positive antibody test
	Who prompted first positive antibody test
	Presenting with seroconversion illness
Risk behaviour	Most likely reasons for HIV infection
	Country of infection
	Self-defined sexual orientation
	Ever injected drugs
	Sexual risk behaviour in last 3 months
Medical History	Ever diagnosed with AIDS
	Current opportunistic infections (OI)
	AIDS-defining conditions
Social circumstance factors	Current partner
	Children
Socio-economic factors	Current housing
	Current employment
	University education
Lifestyle factors	Current smoking status
	Alcohol use
	Recreational drug use
Encounters with UK healthcare providers in year prior to HIV diagnosis	Number of primary care visits
	Number of emergency department visits
	Number of genitourinary clinic visits
	Offered HIV test prior to first positive test

4.2.4.2 *Clinic visit form*

On all subsequent visits to the ICDC, the clinician completes a clinic visit form (Appendix II.). This form is also manually completed and subsequently digitised. The data collected by this form that are relevant to this thesis are shown in Table 4.2.

Table 4.2: Data collected by the routine clinic follow-up form

Variable category	Variable
Identifier	Hospital Number
Visit details	Visit date
Clinical details	Non-AIDS diagnoses
	New AIDS diagnoses
Antiretroviral drug (ARV) prescription details	ARVs prescribed
	ARV start and stop dates
	Reasons for stopping an ARV
Additional information	Free text section

4.2.4.3 ***Prescription data***

Prescription data are collected by the ICDC pharmacy. This data represents the prescriptions issued by the pharmacy rather than prescriptions collected. It includes both the drugs prescribed and the duration for which they were prescribed.

4.2.4.4 ***Routine laboratory data***

Data are collected on T-lymphocyte cell counts (including CD4 cell count), and HIV RNA VL. The T-lymphocyte cell counts are measured using standard flow cytometry techniques[511]. Plasma HIV-1 RNA VL has been measured by several commercially available methods that have changed over time. When VL testing was first introduced in 1996, monitoring was performed using COBAS AMPLICOR HIV-1 MONITOR test 1.0 (Roche Diagnostics, Roche Products Ltd., Welwyn Garden City). Improvements were then made, by the addition of non-B subtype primers; so that the COBAS AMPLICOR HIV-1 MONITOR test 1.5 (Roche Diagnostics) was able to capture non-B subtypes in addition to B subtypes. Improvements in the sensitivity of assays were made to enable lower limits of detection. While the first tests used in the Royal Free had a lower limit of detection of 400 copies/mL, since 1998 most routinely used tests have had lower limits of detection of 40 or 50 copies/mL. More recently at the Royal Free, the COBAS TaqMan (Roche Diagnostics) assay has been used. This assay was accepted for use after formal tests in the laboratory found that the TaqMan and AMPLICOR assays were strongly and linearly correlated and thus considered equivalent[512]. Other assays used at the Royal Free include the LCx (Abbott) and RealTime (Abbott). Again, studies have found a high degree of agreement between these assays[513;514].

4.2.5 **Compilation of the research database**

The research database utilises the information held in the clinic database. Annually, a trained research assistant, Clinton Chaloner, conducts a 100% notes audit of the clinic database. He extracts additional information from the text section of the routine clinic follow-up form and the paper notes, corrects any mistakes, and updates any information that has changed since the last notes audit. The information collected by the note review includes: start and stop dates for each individual ARV; reasons for stopping any ARV; hospital in-patient admissions and discharges with reasons; date and type of AIDS-defining events; date and type of non-AIDS events; known transfers out of the ICDC with centre transferred to if known. If an individual has transferred to the Royal Free hospital from another HIV outpatient clinic, and if the individual gives their consent, then details of previous HIV-related medical history (including laboratory test results) is requested and included in the database wherever possible. This method of notes review means that the database provides a high level of accuracy. In

particular, information that is more complete is available on treatment changes, discontinuations and adherence – with reported ARV interruptions of any length noted in the database, even those as short as 2-3 days. The prescription data and routine laboratory data are transferred electronically from the relevant departments. Sam Hutchinson, who completes Coding Causes of Death in HIV (CoDe) forms on individuals in the database who have died, collects data on deaths in the cohort. This is part of the CoDe project which aims to provide a standardized method for coding the underlying cause of death in PLWH[515]. The RFHCS data is manually entered into the database and the database is securely transferred to Fiona Lampe and Colette Smith in the UCL Research Department of Infection and Population Health.

4.2.5.1 *Data management*

Additional data cleaning steps are then performed to detect and correct inaccurate entries, by checking variable ranges and crosschecking for discrepancies. For example, the sequences of dates (e.g. ensuring drug start dates precede stop dates and that no events occur on a date after the recorded date of death) are investigated. Implausible data are also double-checked, such as checking the antiretroviral treatment information of those receiving mono or dual therapy regimens or five or more ARVs simultaneously in the modern era. Incomplete variables are also completed through other available information where possible: for example, if the gender of a current partner has been completed on the patient registration form, but there is no response to whether the individual has a current partner, then this can be completed as an affirmative response. Finally, searches are made to identify individuals with duplicate hospital numbers, including checking the data of individuals with similar names and dates of birth and asking staff to report any that they identify on an ad hoc basis. Identified potential errors and discrepancies are checked against the paper-based data collection forms.

As I was the first person to use the data from the revised patient registration forms, I played a key role in data cleaning, formatting and the generation of new variables using the methods described above.

4.2.6 **Ethics**

At the time of writing of the thesis, analysis of data from the RFHCS was covered by a letter of approval from the Chairman of the Royal Free Ethics committee.

4.3 **Antiretrovirals, Sexual Transmission Risk and Attitudes (ASTRA) questionnaire study**

The ASTRA study was designed in 2010 in order to examine sexual risk behaviours and attitudes among people diagnosed with HIV and under care in the UK. The main aims of the study included:

- To assess the association of ARV use, current VL suppression, demographic and socio-economic factors, transmission risk beliefs, and other factors, with high-risk sexual behaviour
- To assess the association of questionnaire assessed factors (demographic, socio-economic, symptoms, quality of life, lifestyle and HIV-related factors), with attitudes to starting immediate ART among those who were ART-naïve
- To investigate the association of questionnaire assessed factors (demographic, socio-economic, symptoms, quality of life, lifestyle, HIV-related) with laboratory and clinical outcomes

The methods and participant characteristics have previously been published[516], however, in this section I have summarised the main methods of the ASTRA study.

4.3.1 **Study design**

ASTRA is an observational, cross-sectional self-administered questionnaire study conducted in eight UK NHS HIV outpatient clinics from February 2011 to December 2012, with an additional longitudinal component. The eight centres were Royal Sussex County Hospital (Brighton), East Sussex Sexual Health Service (Eastbourne), Homerton University Hospital (London), Mortimer Market Centre (London), Newham University Hospital (London), North Manchester General Hospital (Manchester), Royal Free Hospital (London) and Whipps Cross University Hospital (London). All participants completed a study questionnaire, and the latest values of CD4 count and VL were recorded by study personnel in a study log for all participants. For consenting participants, linked routine clinical data was provided by each centre using this study log, which contained both the study and clinic numbers. This included clinical data from both before the time of the questionnaire and the time after the questionnaire up until the data was processed to provide to study personnel. Linked data are currently available for six clinics (Brighton, Eastbourne, Homerton, Mortimer Market, Newham, Royal Free) which were collated from 2013 onwards. At the time of this thesis, data was provided up until April 2014 for Brighton, January 2015 for Eastbourne, March 2013 for Homerton, December 2013 for Mortimer Market, October 2015 for Newham, and May 2014 for the Royal Free.

Prior to main study recruitment, a pilot study was conducted at several of the study sites, after which minor changes were made to the questionnaire and information sheet.

4.3.2 **Study population**

PLWH aged ≥18 years and attending one of the eight centres for outpatient care were eligible for inclusion in the study. Individuals were excluded if they were unable to complete the questionnaire in English or French due to language or cognitive difficulties, or because they were too ill or distressed to participate.

4.3.3 **Recruitment**

Within selected recruitment sessions, consecutive individuals attending the HIV outpatient clinics were invited to participate, either while waiting for, or after, their routine clinic appointment. Recruitment took place in each centre over at least a six-month period, as the majority of individuals under care would have been expected to attend the centre over this period. Individuals who were approached and asked to participate were provided with an information sheet about the study (Appendix III.). Those who agreed to participation were asked to sign a consent form (Appendix IV.). This form included an additional optional consent to linkage of questionnaire responses with available routine clinical data.

4.3.4 **Data collection**

The questionnaire was self-administered in the waiting room either before or after the participant's outpatient appointment. In each clinic, a private space was also available to complete the questionnaire, if the participant preferred this. Participants were asked to seal completed questionnaires in the envelope provided and leave in a labelled box in the clinic. Completed questionnaires were stored securely in the clinic and periodically transferred back to the research centre. Although participants were asked to complete the questionnaire in clinic on the day of recruitment to the study, if this was not possible, they could take away a paper questionnaire and post it back using a pre-paid envelope.

There was a separate version of the questionnaire for men (Appendix V.) and women (Appendix VI). The main differences were that only women were asked to record the ages of any children, the HIV status of these children, and whether they were currently pregnant. Men were asked about sexual intercourse with men and women separately, whereas women were only asked about sexual intercourse with men. A French version of the questionnaire was also available if desired.

Identifiable information such as names and clinic identification numbers were not included on the questionnaire, but instead a unique study number was pre-assigned and completed on the first page by the study recruiter, prior to questionnaire completion by the participant. Participants were reassured of the confidentiality of their questionnaire responses, and in particular, that their answers would not be seen by clinic staff or included in their clinic notes.

Study nurses at each of the sites completed a study log for each person approached and asked to participate. Information included the date, study number, clinic number (not provided to research team), consent to participate, and additionally, for those who consented to participate: consent to linkage with clinical data, latest VL and CD4 count and the date that they were measured. The latest value was defined as the last value available to (communicated to) the participant at the time that the questionnaire was issued.

For consenting participants, each study centre used the clinic number in the study log to link the study number to their routine clinical data. Periodically the routine clinical data was securely transferred to the research centre using only the pseudonymised study number for the purposes of confidentiality.

Questionnaires were sent for digitisation to an external data entry company where data were entered twice. Further data checks were performed at the research centre.

Table 4.3 lists the variables collected by the questionnaire that were relevant to this thesis. Table 4.4 lists the routine clinic data provided by clinics for consenting participants that were relevant to this thesis (Appendix VII.).

Table 4.3: Summary of information collected by the ASTRA questionnaire

Variable category	Variable	Response options
Identifier	Study number	
	Clinic	Brighton/Eastbourne/ Homerton/Manchester/ Mortimer Market/Newham /Royal Free/Whipps Cross
Demographic factors	Month and year of birth	
	Sexual orientation	Homosexual/heterosexual /bisexual/other
	Ethnicity	White/black African/other
Socio-economic factors	Financial hardship - able to afford basic needs?	Always/mostly/sometimes/ no
	Employed	Yes/no
	Housing status	Homeowner/renting/ unstable or other
	University education	Yes/no
Social circumstances	Country of birth	UK/non-UK
	Time in the UK	UK-born/>5 years/≤5 years
	English reading fluency	UK-born/fluent/not fluent
	Current partner	Yes/no
	Children	Yes/no
	Supportive network (modified Duke UNC Functional Social Support Questionnaire [FSSQ])	Most/medium/least
Lifestyle factors	Current smoking status	Smoker/non-smoker
	Evidence of alcohol dependency (CAGE score)	Yes/no
	Recreational drug use in the last 3 months	Yes/no
Symptom	Major symptoms of depression (PHQ-9)	Yes/no
	Major or other symptoms of depression (PHQ-9)	Yes/no
HIV-related factors	Month and year of first positive antibody test	
	Most recent CD4 count	
	Most recent VL [a]	
	Most likely reasons for HIV infection	
ART use	Ever on ART	Yes/no
	Month and year ART initiated	
	Started ART because ill	Yes/no
	Ever changed ART because of VL failure	Yes/no
	Currently on ART	Yes/no
	Frequency of taking ART	
ART adherence	Number of doses missed in the last 2 weeks	
	Reasons for non-adherence in last 2 weeks	
	Missed treatment for ≥2 consecutive days in the last 3 months	Yes/no

[a] For those who ever started ART only

Table 4.4: Summary of information collected from linkage to patient notes

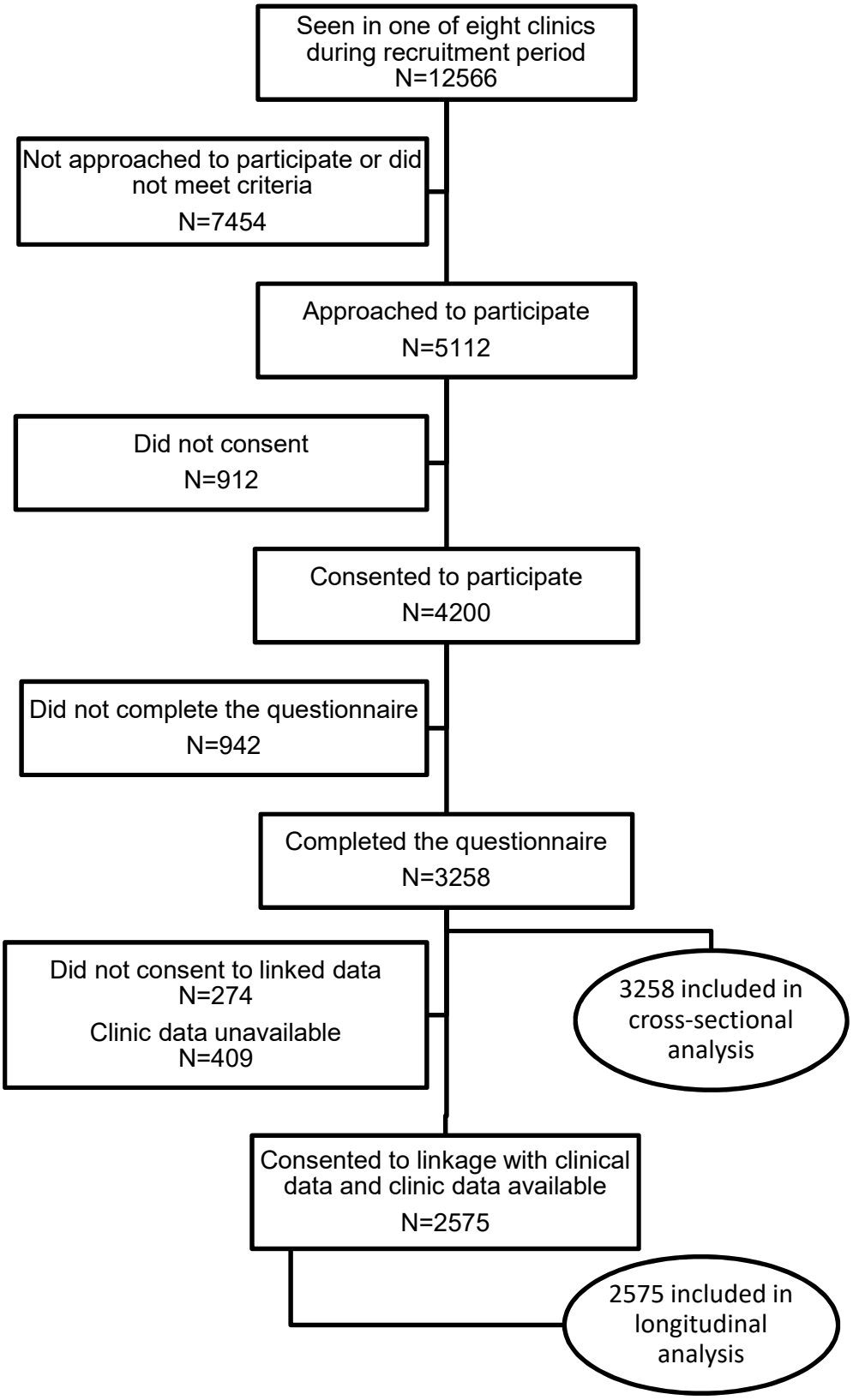
Variable category	Variable
Demographic factors	Month and year of birth
HIV-related factors	HIV exposure category
Clinical details	Date of first HIV clinic visit
	Date of first positive HIV test result
	VL test results [a]
	VL test dates [a]
	CD4 count test results [a]
	CD4 count test dates [a]
	ADE or other clinical diagnoses [a]
	Date of ADE or other clinical diagnoses [a]
	Date of death
ART prescription details	ART drugs prescribed
	Date ART drugs prescribed

[a] All available, before and after the date of the questionnaire; ADE = AIDS defining event.

4.3.5 **Response rates**

An estimated 12566 individuals were seen in the participating clinics during the recruitment period. Of these, 5112 were approached about participating in the ASTRA study and met the eligibility criteria. Of these, 4200/5112 consented to participate and 3258/5112 completed the questionnaire, which gives a response rate of 64% (see flow chart in Figure 4.1). In the six clinics with linked clinic data currently available, 3203 participants agreed to linkage between their questionnaire and clinical data; of those who completed the questionnaire 2575 agreed to linkage with clinical data (2575/4285; which is an overall response rate of 60% for longitudinal analyses in the clinics with available data).

Figure 4.1: Flowchart of ASTRA study participation



4.3.6 **Data management**

Clinic identifiers or contact details were not transferred to the study management centre so that participants were identified only through the pseudonymised study number. All data from the study are stored only on encrypted password protected drives, thus responses are kept confidential.

Participants of the study did not necessarily complete all parts of the questionnaire. In order to have as much complete data as possible, information from clinical records were used to complete any missing information when permission for linkage to routine clinical notes was given and when this information was available. For example missing values for month and year of age, month and year of HIV diagnosis, and ART status information from clinic records was used where possible. For questions with free text answers, these were manually coded into categories as described in Section 4.4.2.

In ASTRA among those on ART, there were 15 individuals with missing data for the adherence question on doses missed in the last two days, and 14 with missing data on whether they had missed two consecutive days of ART in the past three months. For each of these variables, individuals with missing data were included in the adherent category on the basis that there is no indication of non-adherence given.

4.3.7 **Ethics**

Ethical approval for the ASTRA study was obtained via the North West London REC 2 research ethics committee (ref 10/H0720/70).

4.4 **Summary of data used and main variables of interest**

In Sections 4.2 and 4.3 I described the data sources for this thesis: the RFHCS database, including the Royal Free hospital patient registration forms, and the ASTRA study. In this section, I will detail the data used in each results chapter and give details of the main variables used. Table 4.5 summarises which data source is used in each chapter.

Table 4.5: Summary of data used throughout the thesis

Chapter	Data source	N in dataset	N in primary analysis
5	RFHCS	6423	5910
6	RFHCS	6423	1615
7	ASTRA study	Cross-sectional: 3258 Longitudinal: 2983	Cross-sectional: 2405 Longitudinal: 1740
8	ASTRA study	Cross-sectional: 3258 Longitudinal:2983	Cross-sectional: 2405 Longitudinal: 1740
9	RFHCS (Royal Free Hospital patient registration forms)	888	417

In all chapters, the definitions of ART and cART are consistent. ART was defined as a regimen including at least one ARV, whereas cART was defined as a regimen of at least three ARVs (see Section 1.2.1).

As a result of the focused research aims of my thesis (Chapter 3), I used only the variables that were needed to address these specific aims. For example, disclosure of HIV status collected by the ASTRA questionnaire was not included in this thesis since Daskalopoulou et al had already examined this and there was no evidence of disclosure being associated with non-adherence or virological suppression[517]. Study centre was also not included because of confounding with both gender/sexual orientation and SES; therefore adjusting for it would have removed some of the gender/sexual orientation or socio-economic effects that I wished to measure. Furthermore, given post-code data was collected in the patient registration forms, it would have been possible to use area-based measures of SES in addition to the individual-level variables, however, the results from the literature review in Chapter 2 suggested that neighbourhood SES was a poorer marker. The variables considered in this thesis are outlined in detail below.

4.4.1 Derivation of main demographic, socio-economic and lifestyle variables used from the RFHCS

4.4.1.1 *Gender/sexual orientation*

Gender/sexual orientation was defined using gender, and mode of HIV acquisition as a proxy for sexual orientation, as sexual orientation is not routinely recorded in the RFHCS database. On the patient registration forms the only options for gender/sex were male or female. There were fewer than 10 transgender people across the entire cohort and these individuals were classified according to the gender that they identify as. Thus, the three groups were defined as: (i) men who likely acquired HIV through sex with men (MSM), (ii) men who likely acquired HIV through sex with women (MSW), and (iii) women who likely acquired HIV through sex with men. Therefore, individuals in the RFHCS who did not have a sexual mode of acquisition of HIV were unclassified in the gender/sexual orientation variable and excluded.

4.4.1.2 *Ethnicity*

Ethnicity was self-reported to the clinic using standard Self-Defined Ethnicity Codes (SDE) and further classified into a six-category variable: white, black African, black Caribbean, Asian, other/mixed, and unknown.

4.4.1.3 *New Patient status*

New patient status at any point in time was classified using the time between the date of first visit to the ICDC and the date of interest. There were three categories: ≤ six months; six to 12 months; and >12 months.

4.4.2 Derivation of main demographic, socio-economic and lifestyle variables used from the ASTRA study

4.4.2.1 *Gender/sexual orientation*

Gender/sexual orientation was defined using gender, together with responses to questions on sexual orientation and recent sexual behaviour. Given that individuals were given either a questionnaire for men or one for women, and this was used to determine gender, transgender and non-binary gender was not recorded. MSM were defined as men who reported their sexual orientation as gay, homosexual or bisexual (or related term), or those who reported having sex with a man in the past three months. MSW were defined as men who reported their sexual orientation as heterosexual or straight and had not been classified as MSM. Women were defined as women of any sexual orientation (therefore this definition differs from the 'women' category used for the RFHCS, which required sexual transmission of HIV). For a small number of cases, for which sexual orientation could not be classified based on the above definitions, additional information (likely mode of HIV acquisition according to questionnaire or linked clinic data if available) was used to assign a category[518].

4.4.2.2 *Ethnicity*

Ethnicity was defined as a three-category variable: white; black African; other. White and black African or black Caribbean were included in the other category. For individuals who selected more than one category, classification was made based on an individual basis and using responses to country of birth.

4.4.2.3 *Socio-economic factors*

Financial hardship was derived from the question "Do you have enough money to cover your basic needs? (E.g. food, heating)" for which respondents scored 1: "Yes, all the time" 2: "Yes, most of the time" 3: "Yes, some of the time," and 4: "No." For individuals who selected more than one category, they were categorised as the least hardship selection; an average of the selections if they were not consecutive.

Employment status was grouped into two categories for the purposes of this thesis: "employed" includes individuals who reported either full- or part-time employment; "non-employed" includes everyone else with a response to employment status.

Housing status was grouped into three categories: homeowners or owner occupiers; renting, which included those who rented privately or from the council or housing association; unstable/other which included those living in a hostel, shelter, squat, other temporary accommodation, those staying with partners, family or friends, and those who were homeless.

Education was considered as a binary variable: individuals with a university level education or higher; and individuals with below university level education.

Individuals who report "other" to the questions on employment status, housing status or education are categorised into the most relevant category based on any comments in the free text section.

4.4.2.4 ***Social circumstances factors***

Country of birth was defined according to the question "were you born in the UK?" and, if the answer was no, then participants were asked which country they were born in. These were grouped into continents since there were too many countries reported to allow meaningful statistical analysis, and grouped as UK; Europe non-UK; Africa; North America; South America; Asia; Australia; Unknown non-UK.

Time living in the UK was defined as three categories: born in the UK; living in the UK for over five years; and living in the UK for five or fewer years. For *English reading ability*, individuals who are not classified as born in the UK were split into two groups: individuals reporting "fluent" reading ability; and then all other individuals with non-missing data on reading ability. If individuals had missing data for these variables but white British ethnicity recorded, then they were included in the UK-born group.

Supportive network aimed to measure supportive relationships based on a modification of the Duke UNC Functional Social Support Questionnaire (FSSQ)[519]. Participants scored from 1: "much less than I would like" to 5: "as much as I would like," on each of the following five items: whether they have people who care what happens to them; they receive affection; they get chances to talk to someone they trust; they get invited to do things; and they get help when sick. Scores of 5-12 were classified as "least support," 13-24 as "medium support," and scores of 25 as "most support."

Current partner was a binary yes/no variable derived from the question "Are you currently in an ongoing relationship with a partner (wife/ husband or civil partner or girlfriend/ boyfriend)?"

Whether individuals currently have *children* was also considered as a binary yes/no variable. Number of children and any children's ages were not considered since these were only collected among women.

4.4.2.5 ***Lifestyle factors***

Current smoking status was a binary variable derived from responses to questions on whether the participant is a current smoker, ex-smoker, or they have never smoked. Ex-smokers and individuals who have never smoked were defined as a single group since the intention was to consider current lifestyle.

Recreational drug use was defined using binary yes/no responses to the question "in the past three months, have you used recreational drugs? (E.g. poppers, cannabis, cocaine)." If individuals had a missing response to this question then their response was assumed to be a "no."

Alcohol dependency was defined using the CAGE four question alcohol use score[520;521]. The standard definition based on this score was used, so participants with CAGE scores ≥2 were considered to have evidence of alcohol dependency. Individuals with a missing response were assumed not alcohol dependent, except if the whole of the lifestyle section on the questionnaire was blank, and in this case, the response was considered missing.

4.4.2.6 ***Mental health factors***

Depression symptoms were defined using the Patient Health Questionnaire nine item scale (PHQ-9) depression inventory[522]. This is a self-administered questionnaire validated for use in primary care to screen for depression. The standard definitions of "major depression" and "major or other depression" based on criteria were used. *Major depressive symptoms* was defined by an affirmative response to at least five symptom questions, defined as "being bothered or distressed" by the symptom on 'more than half the days' or 'almost every day' in the last two weeks. For the symptom "thoughts that you would be better off dead" an affirmative response also included the category "some of the days". In addition, in order to fulfil the definition the participant was required to have an affirmative response to at least one of two specific symptoms: "little interest or pleasure in doing things" or "feeling down, depressed or hopeless." *Major or other depressive symptoms* was defined by an affirmative response ≥2 symptom questions as defined above, which included an affirmative response to one of the two aforementioned symptoms.

4.4.3 **Derivation of main demographic, socio-economic and lifestyle variables used from the RFHCS patient registration data**

4.4.3.1 ***Gender/sexual orientation***

Gender/sexual orientation was defined using self-reported sexual orientation. Men who reported heterosexual sexual orientation were categorised as MSW. All other men were categorised as MSM, so this group also included a small number of men who have sex with both men and women. The third category was women of any sexual orientation. There were not separate groups for bisexual men and bisexual or lesbian women since there were too few individuals in these categories.

4.4.3.2 ***Ethnicity***

Ethnicity was defined as a three-category variable: white, black African, and other.

4.4.3.3 ***Socio-economic and social circumstances factors***

Employment, *housing status*, and *education* were defined in the same way as for the ASTRA study. *Current partner* and *children* were again defined as binary yes/no variables.

4.4.3.4 ***HIV risk factors***

Reported recent sexual activity was defined using yes/no responses to whether the individual had had any sexual activity in the three months prior to their first visit to the ICDC. Individuals without a response recorded were categorised as “no.”

The risk factor *ever injected drugs* was also defined using yes/no responses, and similarly, individuals without a response were categorised as “no.”

Country of infection was considered as a binary variable where individuals were classified as likely infected in the UK or likely infected outside the UK.

4.5 **Statistical methods**

This section gives an overview of the statistical methods used throughout this thesis. Specific detail of the methods for each analysis are supplied in the methods section of the relevant chapter. SAS version 9.3[523] was used for all analyses with the exception of multiple imputation analyses which were conducted in Stata version 13[524].

4.5.1 **Descriptive statistics**

Provision of summary statistics is important in order to give an overview of the study population. They are particularly valuable for cohort studies since, unlike clinical trials, individuals are not randomised and thus there are likely to be differences between the

groups studied. For categorical variables, the total number of individuals (N) and percentage (%) in each category are reported. For continuous normally distributed variables the mean and standard deviation are reported, or, in the case of skewed distributions, then the median and interquartile range (IQR) are reported.

Incidence is defined as the probability of an event occurring over a given period of time (e.g. diagnoses, deaths, virological rebound). Prevalence is defined as the number of people with a particular condition or factor at a given time. Related concepts are risks, odds, and rates. Incidence risk is the probability that an event will occur by a certain time. Incidence rate is the frequency with which an event occurs in a defined population relative to the person-time at risk. Odds describe the ratio of the probability that an event will occur to the probability that an event will not occur.

4.5.2 **Effect measures**

Effect measures are used to quantify differences between groups and in order to interpret and understand associations. Effect size of an association is commonly measured by a risk ratio (RR) (also known as relative risk), odds ratio (OR), rate ratio, hazard ratio (HR), or prevalence ratio (PR). These are all relative effect measures that express the frequency of an outcome or dependent variable in one group relative to that in another group (see Appendix VIII.).

For each of these effect measures, a value of greater than one indicates an increased risk of the outcome occurring, while less than one indicates a decreased risk of the outcome occurring. If the confidence interval does not include one, then this indicates a statistically significant difference between groups.

4.5.2.1 ***Comparison of the effect measures***

RR is an intuitive measure that is easier to interpret than an OR, although ORs are approximately equal to a RR if the outcome is relatively rare (usually taken as an incidence of below 10%). In cases when the outcome is not rare however, ORs may be falsely interpreted as RRs and thus may exaggerate associations[525]. On the other hand, the main advantage of ORs is that they are not dependent on the prevalence of an event, whereas RRs are[525].

PRs are easy to understand as a comparative measure of prevalence. They can be interpreted in a similar way as the RR, since both can be seen as probabilities – PRs provide information on the relative frequency of an event at a set time and RRs on the relative frequency of an event over a period of follow-up.

In longitudinal analyses where follow-up data is considered, individuals may not be followed for equal lengths of time for many reasons, for example late study entry, lost to follow-up (LTFU), death, cure, etc. Using RR or OR will be misleading if there are a large number of individuals with varying lengths of follow-up so rate ratios would be a more appropriate measure.

4.5.3 **Associations between variables**

Pearson's Chi squared test was used to make comparisons between the groups of a categorical variable, however, if any expected cell count is less than five, then Fisher's exact test was used. For ordinal categorical variables, the Cochran-Armitage test for trend was used. Wilcoxon-Mann-Whitney tests were used for continuous variables, as they were not normally distributed. All tests performed are two-sided. A P-valueless than 0.05 was considered an indication of a statistically significant difference.

4.5.4 **Statistical models**

The choice of which statistical method to use depends on the type of dependent variable (or outcome or response) being considered. The two main statistical models used in this thesis are the modified Poisson regression model, and the Cox proportional hazards regression model.

4.5.4.1 ***Regression analyses***

Regression analysis is a statistical process for estimating the relationships between a dependent variable and one or more independent variables (covariates, explanatory variables or predictors). A family of regression models exist called generalised linear models (GLMs), where the dependent variable is assumed to follow an exponential family distribution with its mean equal to some linear function of the independent variables (see Appendix IX.). Some examples of GLMs are linear (Appendix X.), logistic (Appendix XI.), Poisson, and cox proportional hazards, with the simplest being linear regression.

Poisson regression and modified Poisson regression

Count data is constrained to the range of positive integers only. The Poisson distribution is more appropriate for such data than the normal distribution (used in linear regression), since a Poisson-distributed variable can only take integer values and the mean is positive. Poisson regression is described in Appendix XII. in more detail.

Poisson regression was used in this thesis in two contexts. The first is for binary dependent variables. Although the dependent variable in a Poisson regression is

usually a count, it can also be used in a modified format to model a binary dependent variable (i.e. situations in which the count can only take the values zero or one). Here, the Poisson model is estimating the probability of an event occurring, rather than the odds of an event occurring as done in logistic regression. Therefore, associations with explanatory variables are estimated using RRs. As RRs are intuitive to understand, I have chosen to use this method in my thesis instead of the more traditional logistic regression, which would have produced less easily interpretable ORs.

As mentioned in the previous paragraph, a modification is required for Poisson regression when the dependent variable is binary. A Poisson-distributed variable has an equal mean and variance by definition. In contrast, the mean of a binomial-distributed variable is given by p and its variance by $\mathrm{p}(1-\mathrm{p})$. The variance must be smaller than the mean, as $(1-\mathrm{p})$ is a probability and must be ≤1. Thus, the variance of a binary dependent variable is overestimated in a Poisson regression. To account for this over dispersion, I used the well-established modified Poisson regression model proposed by Zou et al.[526]. In this method, sandwich estimation is used to provide robust error variance, which works by defining subjects as if they have repeated observations even though only one observation is available. Further details may be found in Appendix XIII. and in the paper by Zou et al.[526].

Survival analysis approaches and Cox proportional hazards models

A standard survival analysis approach was used for time to event data. Although the name of survival analysis suggests that the dependent variable should be time to death, it need not be death or even a negative event. Thus, dependent variables such as time to virological suppression or time to virological rebound can also be analysed with this approach. Survival analysis approaches are suitable for data in which the time to event is censored for some individuals. Censored data happens when a measurement or observation is only partially known. In this thesis, I only have situations with right-censored data, although left-censored and interval-censored data can occur. Right censoring refers to the situation when a period of follow-up for an individual ends before the event of interest; we do not know the time-to-event for this individual, only that it had not yet occurred at the last visit. We say that the individual's follow-up is censored as this last visit date.

In this thesis, I have used Kaplan-Meier methods to calculate unadjusted estimates of survival/failure probabilities and compared groups using the log-rank non-parametric test. The associations of explanatory variables with time-to-event dependent variables were investigated using Cox proportional hazards regression (see Appendix XIV.). This model uses the hazard rate (i.e. the instantaneous rate of an event occurring) as

its outcome, and so associations between potential risk factors and the outcome are quantified using the hazard ratio (HR). The main advantage of this method over Poisson regression is that it is semi-parametric: it makes no assumption about the shape of the underlying hazard function. In other words, it puts no restrictions on how the rate of the event changes over time; it only requires that the ratio of hazards between exposure groups remain constant over time. This is known as the proportional hazards assumption.

4.5.4.2 *Generalised estimating equations*

GLMs with Generalised Estimating Equations (GEEs) can be used to model data with a clustered dependent variable[527;528]. In this case, not all observations are independent of each other, and a major assumption of GLMs no longer holds (see Appendix IX.). In my thesis, I encountered clustered data when including repeated measurements, for example when including the virological response of an individual at a number of different time-points in the same analysis. Here, responses from the same individual (cluster) are likely to group together (be correlated), whereas responses from different individuals are likely to be independent. In this situation, standard GLMs may underestimate standard errors due to false inflation of information, as it assumes all observations are independent and does not account for this correlation between responses from the same individual. Inclusion of GEEs in a regression model is a way of accounting for this by explicitly specifying the structure of this additional correlation. A more detailed explanation of GEEs and different correlation matrices is included in Appendix XV. and in a paper by Zeger et al.[529].

Regression models with GEEs estimate mean, or population average, responses. The parameters obtained from this model can be interpreted similarly as for a standard GLM; for example, ORs are obtained from a logistic regression. However, they now refer to the average response in the population. For example, an OR obtained from a GLM with GEEs estimates the effect of a unit increase in the independent variable on the average response of the population.

4.5.4.3 *Linear contrasts*

When summarising the association between a categorical variable and a dependent variable, one of the categories is usually chosen as the reference. The risk of an event in the other categories is then estimated compared to this reference group, for example by presenting a RR. However, the choice of reference group is relatively arbitrary and can be changed without fundamentally altering an analysis. When considering the association of gender/sexual orientation with the outcomes considered in this thesis, I wished to present each pairwise comparison rather than choosing a

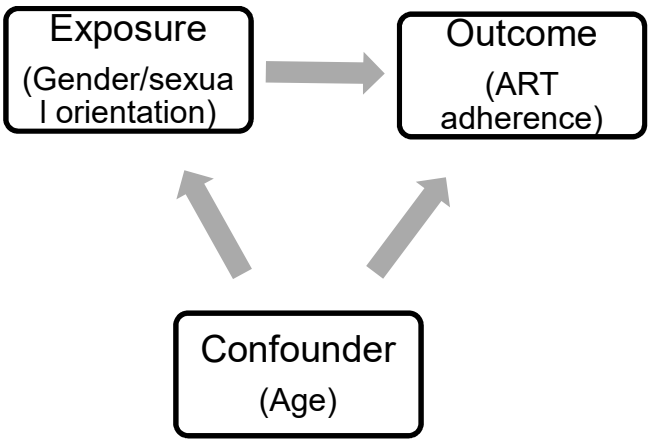
specific reference group. Therefore, I used a linear contrast, which is a linear combination of variables whose coefficients add up to zero. This enabled me to define pairwise comparisons for MSW vs. MSM, women vs. MSM, and women vs. MSW all from the same regression model.

4.5.5 **Confounding variables, mediating variables, statistical interaction, and collinearity**

4.5.5.1 ***Confounding variables***

A confounding variable is one which (i) is independently associated with the dependent variable; (ii) is associated with the exposure of interest; and (iii) does not lie on the causal pathway between the exposure and dependent variable (i.e. it is not a result of the exposure and a risk factor for the dependent variable). Though confounding is not an issue for randomised studies as condition (ii) cannot hold by definition, it is frequently a major issue in observational studies. Confounding can either mask or falsely induce an association between the exposure of interest and the outcome. For example, consider the association between ART adherence and gender/sexual orientation. Here, age is a potential confounder, since men living with HIV tend to be older than women are and younger age is a risk factor for poorer ART adherence[375;530-533] (Figure 4.2).

Figure 4.2: Illustration of confounding using a causal diagram

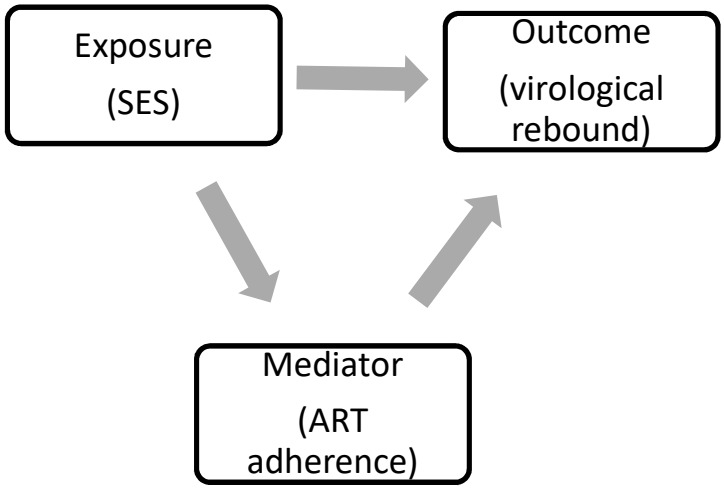


4.5.5.2 ***Mediating variables***

A mediating (or intermediary) variable is one that is on the causal pathway between an exposure and outcome being investigated. In other words, a variable that follows the exposure but precedes the outcome in a causal chain. For example, ART adherence may be a mediating variable for the association between SES and virological rebound, as lower SES status could lead to lower adherence, which in turn leads to a higher risk

of virological rebound. Mediating factors represent an indirect effect of the exposure on the outcome as represented in Figure 4.3.

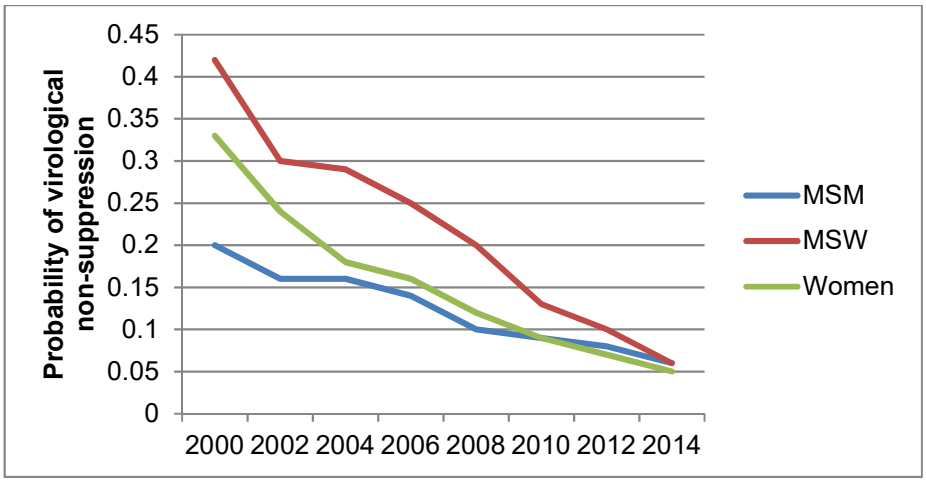
Figure 4.3: Hypothetical illustration of mediating factors using a causal diagram



4.5.5.3 ***Statistical interaction***

An interaction between variables occurs when a relationship between two variables is modified by at least one other variable, i.e. the strength or direction of an association between two variables is different depending on the level of an additional variable. For example, there may be large differences in the percent with virological non-suppression in the different gender/sexual orientation groups in earlier calendar years, but these differences may no longer be present in later years; here gender/sexual orientation and calendar year interact. This hypothetical example is represented graphically in Figure 4.4.

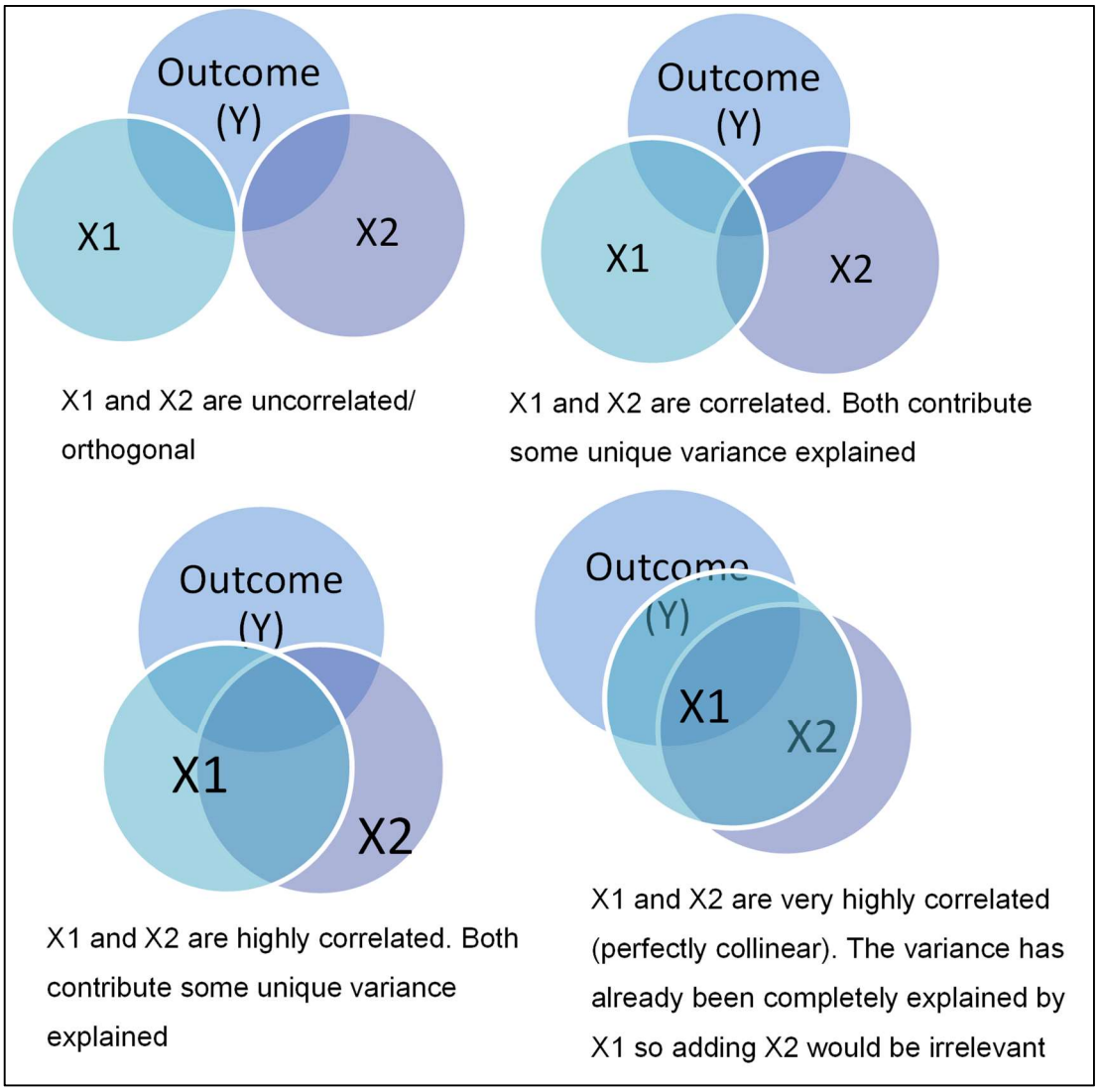
Figure 4.4: Hypothetical illustration of statistical interaction



4.5.5.4 *Collinearity*

Collinearity refers to the situation in which two or more independent variables in a multivariate model have a tendency to vary together (i.e. they are highly correlated); this is illustrated in Figure 4.5. For example, different markers of SES, such as financial hardship and employment, are likely to be highly correlated. When the association of one dependent with two or more explanatory variables are considered simultaneously, the more highly correlated the variables are, the more difficult it is to distinguish how much of the variation in the outcome each is accountable for. The consequences are that the estimated coefficients will have large standard errors, estimates of effect size may be irregular, and it is difficult to distinguish the effect of the individual collinear variables on the outcome.

Figure 4.5: Illustration of collinearity between variables (X1 X2) [a] and of variance explained [b]



[a] Overlap between X1 and X2 illustrates the correlation between them; [b] overlap between the outcome and either X1 or X2 represents the proportion of the variance in outcome that can be explained by that variable.

4.5.6 **Approaches taken in this thesis to account for confounding, statistical interaction, and collinearity**

4.5.6.1 ***Methods for handling confounding***

In this thesis, I have used one of the most common ways for accounting for confounding by using multivariable regression analysis. These models provide adjusted estimates of effects (such as RRs, ORs and PRs) which enables one to estimate the association between a specific independent variable and a dependent variable, holding all other independent variables constant[534].

4.5.6.2 ***Methods for handling statistical interaction***

In this thesis, I have used regression models to investigate presence of statistical interactions, by adding an interaction term (the product of variables) alongside the independent variables. If the hypothesis test for this interaction term reaches statistical significance, then it implies that the coefficient the interaction term is different from zero. In other words, the effect of one explanatory variable on the dependent variable differs according to the value of the second explanatory variable. Thus, the effects of each independent variable has to be presented conditional on the level of the second independent variable (e.g. multiple estimates of the association between gender/sexual orientation should be presented, which will differ according to calendar year and vice versa).

4.5.6.3 ***Methods for handling collinearity***

Two common approaches to collinearity in regression models are: (i) combining highly correlated explanatory variables into one explanatory variable (or a small number of uncorrelated variables); and (ii) only including a subset of the correlated variables in the model at any one time. The first situation can be applied by employing methods such as principal component analysis (PCA) or partial least squares regression, which use orthogonal transformations to convert a set of potentially correlated variables into linearly uncorrelated variables. However, as this can lead to explanatory variables that are difficult to interpret clinically, I have decided to take the second approach.

There are two situations that I have encountered in my thesis where collinearity was a particular issue. Firstly, there are high levels of collinearity of both ethnicity and clinic of recruitment with the covariates of interest; namely gender/sexual orientation and SES, throughout the thesis. In the UK, ethnicity is very strongly associated with gender/sexual orientation, as for example a large proportion of MSM are of white ethnicity, whereas a large proportion of MSW are of black African ethnicity. Thus, disentanglement of the effects of gender/sexual orientation and ethnicity is not straightforward. In the ASTRA study, the clinic of recruitment is strongly correlated with

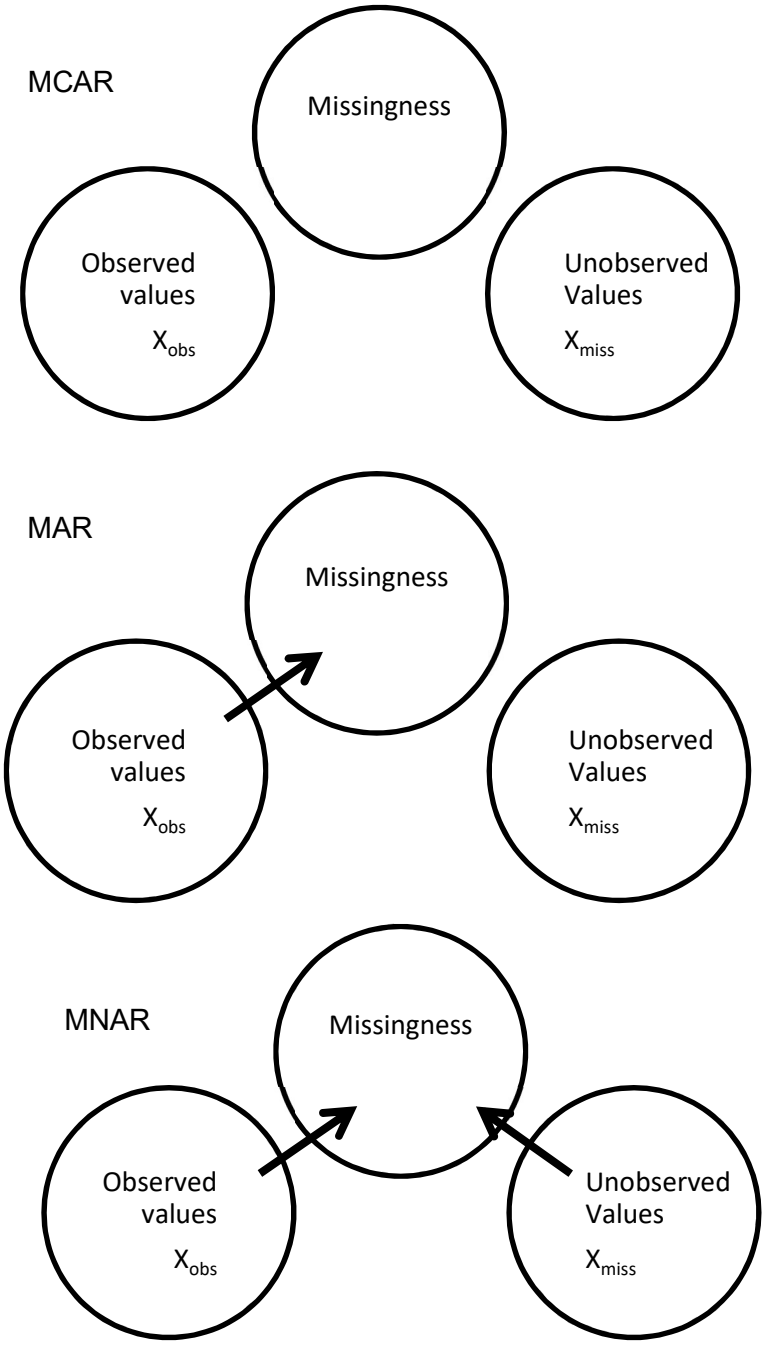
gender/sexual orientation (e.g. Mortimer Market had a higher proportion of MSM than the other clinics), and with socio-economic factors due to the clinic's geographical locations. As gender/sexual orientation and SES are the focus of this thesis, I have therefore not included ethnicity and clinic in multivariable models.

Secondly, in Chapters 7 to 9, I have considered different markers of socio-economic status in separate regression models in the majority of cases. The main reason for this is because they are highly correlated with each other (see Section 7.4.1), but it is also that I am interested in the individual association of each SES marker with virological and late diagnosis outcomes, regardless of how much of this effect is independent of other SES markers. The one exception to this is in Chapter 8 where I have used stepwise regression to select a subset of variables to include in a model. Stepwise regression fits regression models using an automatic procedure to select which independent variables to include. At each step, a variable is considered for addition to or subtraction from the independent variables in the model based on some pre-specified criterion[535]. More detail will be given in Section 8.3.5.

4.5.7 **Handling missing data**

Missing values for dependent and independent variables can cause biased estimates, biased standard errors and inefficiency. It is possible to classify types of missing data into: Missing Completely At Random (MCAR), Missing At Random (MAR) or Missing Not At Random (MNAR). If the probability that data are missing does not depend on the values of the observed or missing data, then the data are MCAR. In other words, data are MCAR when there is no systematic reason why data are missing, other than random chance. In contrast, data being MAR is much more common, and occurs when the probability of being missing depends only on observed data. For example, if data on SES were more likely to be missing in men than women, and this were the only reason (other than chance) for it to be missing, then data on SES would be MAR, providing information on gender was also available in the dataset. Finally, MNAR is the situation when the probability of being missing depends on both observed and missing data. For example, if data on SES were missing depending on the level of SES itself (so those of lower SES were less likely to complete the responses to these questions) then these data would be MNAR, as it would depend on a factor that was unobserved. Figure 4.6 illustrates the different missing data mechanisms.

Figure 4.6: Missing data mechanisms [a]



[a] Arrows indicate association

There are ways to distinguish whether data are MAR rather than MCAR (for example comparing the characteristics of individuals with observed data and individuals with missing data). However, there is no statistical way to test whether the data are MNAR rather than MAR so it is necessary to make a judgement based on knowledge of the situation.

There are two methods used in this thesis to deal with the issue of missing data: Complete-Case analysis (CC) and Multiple Imputation (MI).

4.5.7.1 *Complete-case analysis*

Complete-case analysis is a method whereby only individuals with complete data are included in the analysis, and individuals with missing values are excluded. This method may be employed when few data are missing. Thus omitting cases would not severely diminish the analysis population, and would be unlikely to cause significant bias. However, note that in multivariable analysis, if an individual has missing information on the dependent variable or any of the independent variables being considered, then their entire record is necessarily excluded from analysis. Thus, small amounts of missing data across a range of variables can lead to large amounts of missing data overall.

4.5.7.2 *Multiple imputation*

Multiple imputation by chained equations (MICE) is a method whereby missing data are completed using an iterative process[536]. Each missing observation is assigned (imputed) an initial value using some arbitrary method, for example the mean for that variable. These values are then replaced in turn using univariate imputation models, i.e. regression of the observed values of that variable on all other observed and currently imputed variables. This model may be improved by including auxiliary variables – these are variables which are not a part of the analysis model of interest but that predict either the incomplete variables or the probability that they are missing. It is an iterative process, performed until the dataset is complete with no missing data a process which is then repeated to result in a number of imputed datasets (say m datasets). The main analysis is performed on each of the imputed datasets, resulting in m estimates of the RR/OR/PR. These are then combined into a single overall estimate of the association being studied using Rubin's rules[537].

Before undertaking MI, some details require consideration. The literature suggests that m should be at least equal to the proportion of incomplete cases (so, if 20% of data are missing in a dataset, then 20 imputed datasets should be created)[536;538]. Monte Carlo error (MCE) can be used to determine an adequate number of imputations to obtain stable results[536]. MCE reflects the variability in the results across the imputed datasets due to using a finite number of imputations. The MCE for the estimates, test statistics and the p values need to be sufficiently small in order to make reasonably reliable inferences following the imputation of the missing values. The literature suggests that the MCE of all estimates should be <10% of the corresponding standard error and MCEs of the test statistics should be approximately 0.1[536]. Secondly, a sufficient number of the initial imputations should be discarded such that the estimates will be unaffected by the arbitrary method used for the first imputation and the process will have converged to produce stable estimates. This is called the burn-in period. It is

also important to take into account the potential presence of perfect prediction – there is a level of a categorical variable for which the outcome is certain to occur/not occur. This calls for a few low weighted observations to be added to the data set so that no prediction is perfect (augmented regression), in order to avoid biased results.

It is possible to account for the bias caused by data being MNAR using MI methods with weighted Rubin's rules. However, this requires knowledge of the nature of the missing data and reasons why they are missing. As this is usually difficult to ascertain, one needs to make assumptions, which adds uncertainty to the results and are often unverifiable.

4.5.7.3 ***Choice of method for handling missing data***

MI is a more efficient analysis method compared to CC because all cases are included, thus the estimates of associations are likely to be more precise. This is particularly true for situations with a large proportion of missing data[539]. However, when the missing data mechanism is MCAR then CC has been shown to lead to unbiased estimates of association and is a much simpler method to use. Under the MAR missing data mechanism, MI has negligible bias, whereas CC is biased because it ignores systematically missing data. However, there are other situations in which CC has negligible bias, such as when the variables in the model are either uncorrelated or the correlation between them is small. In data which has missing values for the response variable, in general CC would be used because it does not add any value to the analysis to include these cases, except when auxiliary variables are available for imputation[540;541]. It is often unclear which of MI or CC are more appropriate for the missing data mechanism[539], thus it may be helpful to evaluate the results of both approaches.

Chapter 5 Trends in prevalence of virological non-suppression according to gender/sexual orientation in a UK clinic population 2000-2014

5.1 Objectives

- To present descriptive data on the trends over calendar time by gender/sexual orientation in demographic factors, ART use, type of ART regimen used, CD4 count, VL, hospitalisations, AIDS events, and death among a whole UK HIV-clinic population (the Royal Free HIV Cohort Study) from 2000 to 2014.
- To assess the trends over calendar time in the prevalence of virological non-suppression among all cART treated individuals in the clinic population
- To assess whether any trends of calendar time differed by gender/sexual orientation.

5.2 Introduction

The composition of the HIV-diagnosed population in the UK has changed over time in terms of demographic characteristics[210;542]. Although the number of new HIV diagnoses among heterosexual individuals in the UK is now decreasing, heterosexually infected individuals make up a greater proportion of people living with HIV (PLWH) and accessing care than MSM[543]. It is vital to examine changes in the HIV epidemic over time in order to understand the demographic make-up and clinical characteristics of the HIV-positive population accessing care in the UK. The description of an HIV-clinic population presented in this chapter also serves as a documentation of the characteristics of the Royal Free HIV Cohort Study (RFHCS) on which the subsequent analyses in this chapter and the analyses in Chapters 6 and 9 were based. This allows additional insights into the generalisability, interpretation and implications of the results presented in these chapters. There have been substantial improvements in the prognosis for PLWH over time in high-income countries[60;543-550]. This includes evidence of improved virological and immunological responses to ART in previous studies of the Royal Free HIV cohort[59;365;551]. These improvements may be a result of: increasingly efficacious and less toxic antiretroviral drugs (ARVs) and regimens[546-548]; a greater number of treatment options; better management of toxicities; recommendations not to interrupt treatment[162]; a greater appreciation of the importance of treatment adherence and additional adherence support; guidelines to initiate ART at an earlier stage[135;552-554]; and reductions in late diagnoses[543]. However, such improvements in treatment success may not necessarily have occurred equally across the gender/sexual orientation groups. Even in the most recent years,

heterosexual men and women have a high prevalence of late diagnosis[210;543], and treatment disruptions remain more common among women compared to men[126;189;362]. Such factors may influence the success of treatment and contribute to disparities in response between MSM, MSW and women.

Chapter 2 highlighted several studies examining the effects of gender/sexual orientation on virological response amongst those initiating ART (see Section 2.4), and this question is addressed in the RFHCS in Chapter 6 of this thesis. However, in addition to studies focussing on sub-populations such as those starting ART, it is also important to study virological status among all people with diagnosed HIV, using entire clinic populations, in order to get a more comprehensive picture of the success of clinical care and treatment. A number of studies have addressed the wider issue of immunological and virological status among representative populations of HIV-diagnosed individuals under routine care, regardless of time spent on ART[355;356;359;364;365]. All observed a higher probability of virological non-suppression among heterosexual individuals on ART compared to MSM. In particular, a previous study of the Royal Free HIV cohort from 1999 to 2004 found a decrease in prevalence of VL >50 copies/mL over calendar time, but found that on average black African heterosexual men had a 30% higher prevalence of non-suppression compared to MSM receiving ART for ≥24 weeks[365]. In addition, there was no evidence that the differences between these two groups were narrowing over calendar time. However, this study did not directly compare women with either MSM or heterosexual men. Furthermore, the results relate to a period more than 10 years ago and may no longer be representative of trends or gender/sexual orientation differences in prevalence of VL non-suppression. Therefore, it is important to assess whether gender/sexual orientation disparities in ART response have narrowed or widened with time in the clinic population as a whole.

5.3 **Methods**

5.3.1 **Study population**

All individuals in the RFHCS who attended the Ian Charleson Day Centre (ICDC) at the Royal Free Hospital (i.e. attending for care) at least once between 1 January 2000 and 31 December 2014 with a recorded sexual route of HIV acquisition were included. January 2000 was chosen as the threshold ART initiation date for inclusion in the analysis since ritonavir boosting of PIs was established as an efficacious ART component[53] and VL assays with a lower limit of detection of 50 copies/mL were in

routine use by this time. At the time of the analysis, the last complete year for which there had been a clinic notes review was 2014. I excluded individuals who acquired HIV through a non-sexual route, e.g. intravenous drug use (IDU), as there was no information to use as an indicator of sexual orientation for these individuals. In line with the UK HIV-positive population as a whole, only a small proportion (6%) of the cohort had a non-sexual or unknown mode of HIV acquisition.

5.3.2 **Outcomes of interest**

In order to address the first aim of this chapter, trends over time by gender/sexual orientation in the following outcomes were considered:

- Age: for each year as that on the 1st July, this was calculated using date of birth.
- Ethnicity: self-reported and, for the purposes of this analysis, categorised into six groups: white, black African, black Caribbean, Asian, mixed/other, and unknown for individuals with missing data.
- ART use: on ART was defined as on at least one ARV at the time of the VL or CD4 count measurement closest to the middle of that calendar year.
- ART regimen: the number of drugs in the regimen, the specific Nucleoside Reverse Transcriptase Inhibitors (NRTIs) used, and the ARV drug classes in the regimen.
- CD4 count: using the measurement closest to the middle of that calendar year.
- VL: using the measurement closest to the middle of that calendar year.
- Hospitalisations: rate calculated as the frequency of hospitalisations in a particular year divided by the total follow-up time and multiplied by 100. Multiple hospitalisations per individual were permitted. Events at presentation were included, as long as they did not occur more than two weeks before the date of first visit to the ICDC.
- AIDS events: rates were calculated in the same way as for hospitalisations. Multiple AIDS events were permitted but repeated re-occurrences of the same specific AIDS event that an individual had previously experienced were not included. Events at presentation were included, as long as they did not occur more than two weeks before the date of first visit to the ICDC.
- Death: rates were calculated as the number of deaths in a particular year divided by the total follow-up time and multiplied by 100.

In order to address the second and third aims of this chapter, a single outcome of virological non-suppression was considered, defined as a VL >50 copies/mL. A cut-off

of 50 copies/mL was used primarily because it was the lower limit of detection of the VL assays used most frequently over the follow-up period, and also because UK guidelines state that achievement of a VL <50 copies/mL is the goal of treatment[552]. A higher cut-off was not used as a recent study suggests even a single VL between 51 and 199 copies/mL is strongly predictive of subsequent virological rebound[555].

5.3.3 **Inclusion criteria**

To be included in analyses for a particular year, an individual was required to have attended HIV services at the Royal Free Hospital for care in that year. Presence of either a CD4 count or VL measurement was used as a proxy for clinic attendance, as both were routinely measured at each visit over the study period. Individuals could be included multiple times if their attendance spanned more than one calendar year, however, only one CD4 count and VL measurement per individual per year was included. This is because frequency of monitoring may be dependent on the CD4 count and VL values. For example, individuals with an unsuppressed VL (as per current UK recommendations[552]) or those with advanced disease are likely to be more closely monitored. Thus, a single value per year was considered to ensure that these groups were not over-represented. The measurement chosen was the one measured closest to the mid-point of the year of interest (1st July).

Different entry criteria were used for analyses with clinical outcomes (AIDS events, hospitalisations and death), which took a person-years approach. Here, individuals were followed from the date of their first attendance at the Royal Free Hospital, until the earliest of 31st December 2014, death, or last clinic visit.

For the second half of this chapter, formally assessing trends over time in prevalence of virological non-suppression, two sub-populations were considered: (i) for each calendar year, individuals who attended the clinic in that year and had been on continuous cART for at least the six months prior to the date of the VL measurement were included (individuals would be excluded if they stopped taking at least three ARVs within this period); (ii) for each calendar year, individuals who attended the clinic in that year and had ever started cART at least six months previously, regardless of any current treatment interruptions or disruptions, were included. The second sub-population was chosen to reflect the current paradigm, based primarily on the results of the SMART study[162], that once started, cART should not be discontinued. As such, the aim is for all individuals who have ever started cART to have a suppressed VL. As the SMART study results were released in 2006, this analysis was restricted to 2006-14. The six-month window was chosen to allow individuals the potential to achieve

virological suppression; most individuals would be expected to have attained this after this length of time[367;556-560].

5.3.4 **Covariates of interest**

The two main covariates of interest were gender/sexual orientation and calendar year. Gender/sexual orientation groups MSM, MSW, and women were defined as explained in Section 4.4.1.1 . Calendar year was used as a continuous variable (to estimate an average trend over time) in each statistical model, and was used as a categorical variable in graphical representations.

5.3.5 **Statistical analyses**

First, the percentage of the clinic population that were MSM, MSW and women in each calendar year was presented. Then, for categorical variables, proportions by calendar year and gender/sexual orientation were presented graphically. For age, the median, interquartile range (IQR) and range for each gender/sexual orientation group in each calendar year was displayed using box plots.

For hospitalisation, AIDS events, and death crude incidence rates per 100 person-years and corresponding 95% confidence intervals (CIs) were calculated, stratified by calendar year of follow-up. CIs were calculated using the exact Poisson method if ≤20 events occurred, and with a normal approximation otherwise.

The prevalence of virological non-suppression for each gender/sexual orientation group in each year was calculated for the two sub-populations. Modified Poisson regression was used to obtain prevalence ratios (PR) for the association of the covariates with virological non-suppression. Generalised estimating equations (GEEs) were used to account for the repeated observations for each individual. The correlation structure selected was autoregressive(1) to allow for stronger correlation between nearer time points. The association of the two main covariates of interest, gender/sexual orientation and calendar year, with the prevalence of virological non-suppression was assessed first in a model only including these two explanatory variables. A second model additionally adjusted for age (as a continuous variable) and new patient status, defined as the time between the date of first visit to the ICDC and date of VL measurement. This was categorised into three groups: ≤six months; six to 12 months; and >12 months. This variable was included because a previous study in this cohort suggested that new patient status was an important confounder for the association between demographic group and raised VL[365].

Treatment guidelines on when to start cART[50;133;134;136;137;142] and treatment regimens prescribed[548;561-563] have changed considerably over the study period. As the study population includes both those newly starting cART and those on long-term cART, CD4 count at cART initiation and cART regimen are likely strongly associated with calendar time. Thus, I did not adjust for CD4 count at cART initiation or type of cART regimen, as I wished to capture (rather than eliminate) the effect of these factors in the assessment of trends, as some of the calendar effects are likely mediated through these two factors.

A test for linearity of the association between calendar year and virological non-suppression was conducted by including a quadratic term (i.e. adding a squared term to the model in addition to the linear term). If this quadratic term suggested a non-linear association, then the association of calendar time with prevalence of virological non-suppression was modelled using a piecewise linear slope, as I felt that this parameterisation would be easier to interpret than a quadratic term. The time point(s) at which the slope changed gradient were determined by visual examination. If there was no evidence that inclusion of a quadratic term improved the model fit, then the association between calendar time and virological non-suppression was modelled as a single linear slope.

Differences in the trend over time in virological non-suppression by gender/sexual orientation were assessed using tests for interaction.

The proportion lost to follow-up (LTFU) (including having a substantial period of non-attendance) was also assessed. An individual was considered LTFU in a particular year if they had a recorded VL in that year, had the potential for a further two years of follow-up, and had no VL measurement in those subsequent two years. In order to capture both temporary and long-term LTFU, individuals were defined as LTFU even if they had subsequent VL measurements recorded after a gap of two years. It was only possible to calculate this up until 2012 since there were not two subsequent years of data available for 2013 and 2014. LTFU was analysed for the two sub-populations defined previously in Section 5.3.3, thus the denominators were all those with a VL recorded (i.e. attending the clinic) in any one year who (i) were currently on cART; or (ii) ever started cART.

5.3.6 **Sensitivity analyses**

As a sensitivity analysis, all analyses were repeated, re-defining virological non-suppression as a VL >200 copies/mL. Although attaining virological suppression to <50 copies/mL would be considered the initial goal of treatment from a clinical

perspective, the reason for considering a threshold of 200 copies/mL was that low level viraemia may not be indicative of true virological failure[564].

5.4 **Results**

5.4.1 **Trends over time in the characteristics of HIV-positive individuals**

The number of individuals attending the Royal Free Hospital with a likely sexual mode of HIV acquisition has increased from 1262 in 2000 to 2894 in 2014. There were increasing numbers in all three gender/sexual orientation groups, although MSM remained the largest group compared to MSW or women (Table 5.1). An increasing percentage of individuals attending for care were MSW or women.

The first column of Table 5.1 displays the denominators for the first results section in this chapter, considering the trends in the characteristics of all individuals under care. The second and third columns give the denominators for the two study populations considered for the virological non-suppression analyses.

Table 5.1: Number of HIV positive individuals who attended the HIV outpatient clinic at the Royal Free Hospital for care 2000-14 [a]

Year	Number (%) in attendance [b]							Number in attendance [b] currently receiving cART [c]				Number in attendance [b] and ever received cART [c] [d]			
	MSM		MSW		Women		Total	MSM	MSW	Women	Total	MSM	MSW	Women	Total
2000	848	67%	159	13%	255	20%	1262	451	82	113	646	-	-	-	-
2001	928	65%	196	14%	296	21%	1420	526	99	131	756	-	-	-	-
2002	1065	65%	239	14%	346	21%	1650	604	131	183	918	-	-	-	-
2003	1153	63%	268	15%	421	23%	1842	699	164	221	1084	-	-	-	-
2004	1241	62%	298	15%	451	23%	1990	778	201	261	1240	-	-	-	-
2005	1355	62%	319	15%	511	23%	2185	887	220	308	1415	-	-	-	-
2006	1401	61%	332	15%	553	24%	2286	971	236	349	1556	1047	249	399	1695
2007	1461	61%	358	15%	586	24%	2405	1017	271	402	1690	1091	280	453	1824
2008	1508	59%	405	16%	638	25%	2551	1126	297	439	1862	1191	312	502	2005
2009	1571	60%	412	16%	652	25%	2635	1205	322	488	2015	1274	341	542	2157
2010	1591	59%	419	16%	671	25%	2681	1284	339	527	2150	1337	350	575	2262
2011	1615	59%	429	16%	695	25%	2739	1322	353	553	2228	1372	366	601	2339
2012	1658	59%	441	16%	732	26%	2831	1400	373	598	2371	1450	385	639	2474
2013	1699	59%	456	16%	745	26%	2900	1452	398	632	2482	1500	411	664	2575
2014	1695	59%	465	16%	734	25%	2894	1390	384	598	2372	1439	395	619	2453

[a] Individuals could be included at more than one time point; [b] defined as a recorded CD4 count and/or VL measurement in that year; [c] cART = antiretroviral therapy consisting of ≥3 antiretroviral drugs; [d] this analysis considered the years 2006-2014 only.

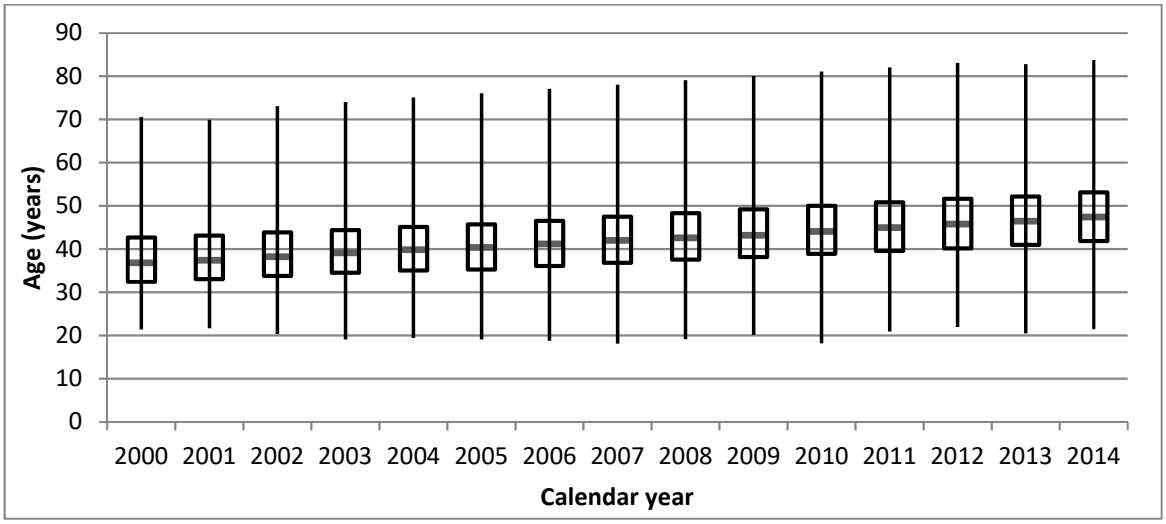
5.4.1.1 *Demographic characteristics*

The median age of PLWH increased in all three gender/sexual orientation groups from 2000 to 2014 (Figure 5.1a-c). In 2000 the median age was 37, 38, and 35 years for MSM, MSW and women, respectively, rising to 48, 49, and 45 years in 2014. MSW had a consistently older median age compared to MSM, and the median age among women was consistently lower than that of both male groups.

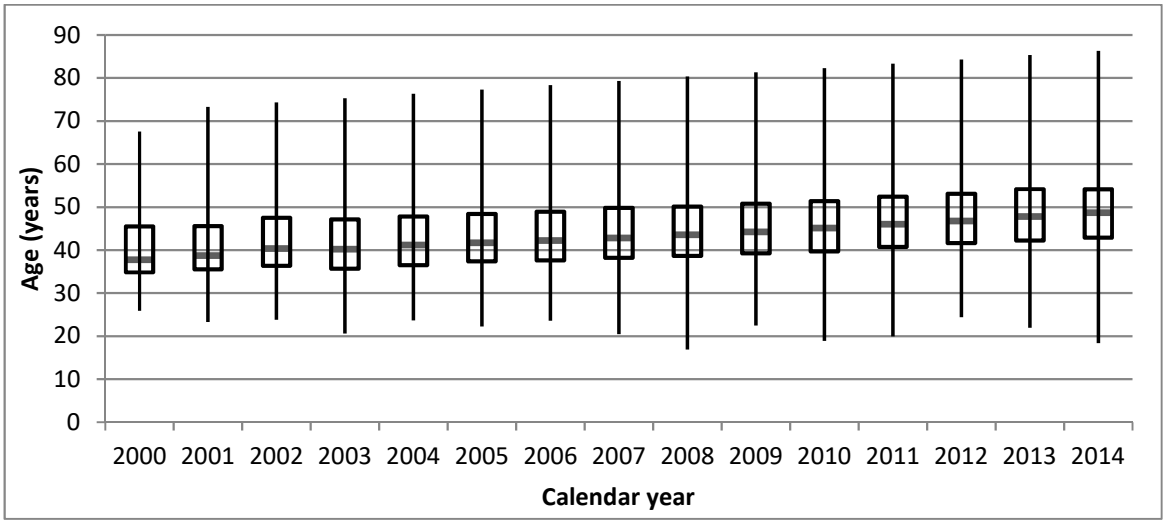
Figure 5.2a-c show the distribution of ethnicity among MSM, MSW, and women, respectively. Most MSM were of white ethnicity and most MSW and women were of black African ethnicity across all years. The proportion of individuals of white ethnicity decreased over time in all groups: 86% of the MSM in 2000 were white compared to 82% in 2014; the corresponding figures were 31% and 26% for MSW and 25% and 18% for women. The percentage of individuals of other/mixed ethnicity remained small but increased in all groups over the study period.

Figure 5.1: Box plots of age among all individuals attending for care by gender/sexual orientation 2000-14 [a b]

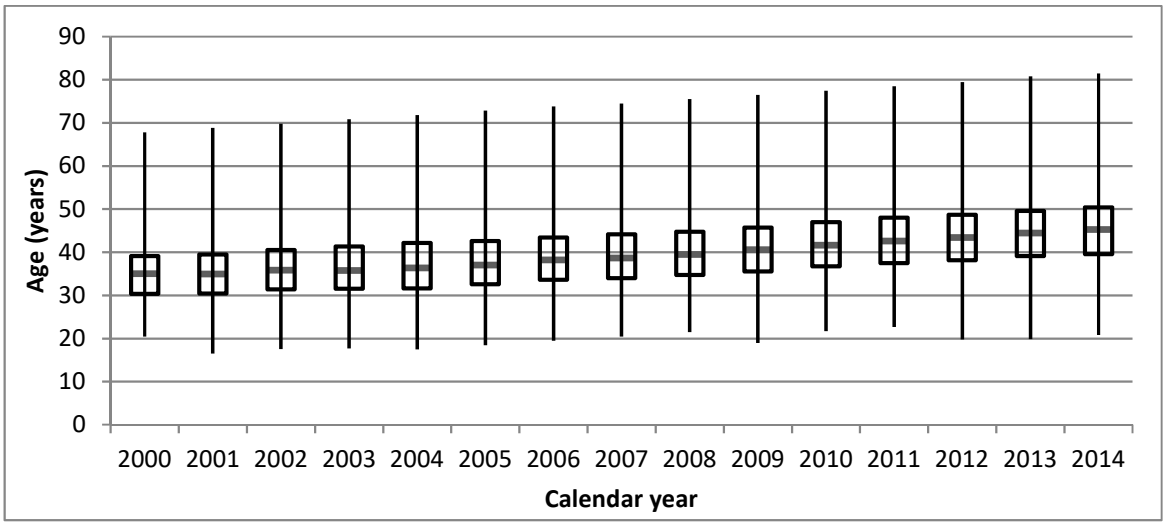
a): MSM [c]



b): MSW [c]



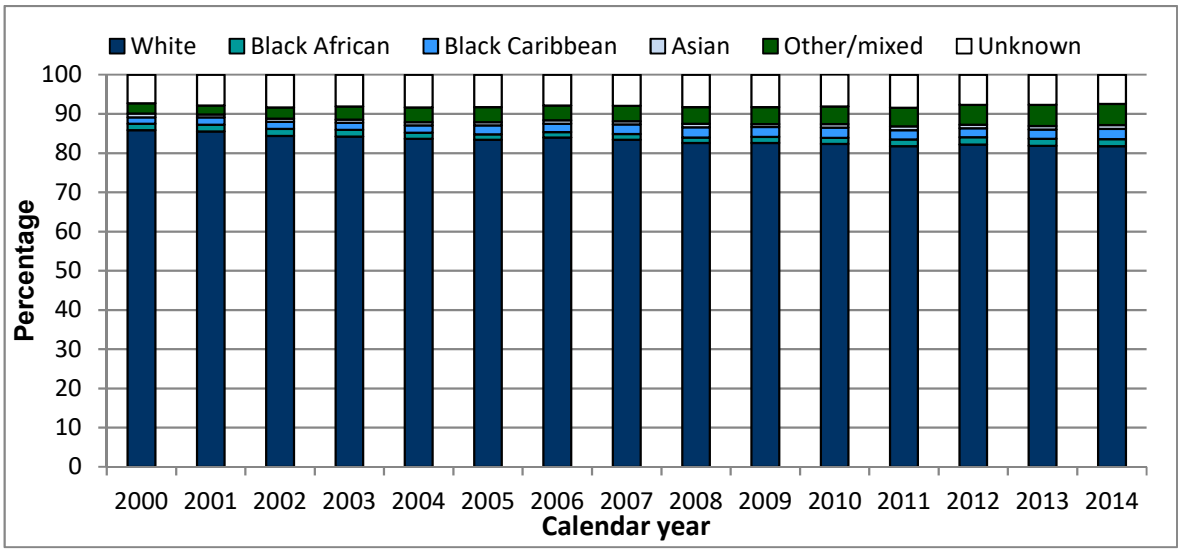
c): Women [c]



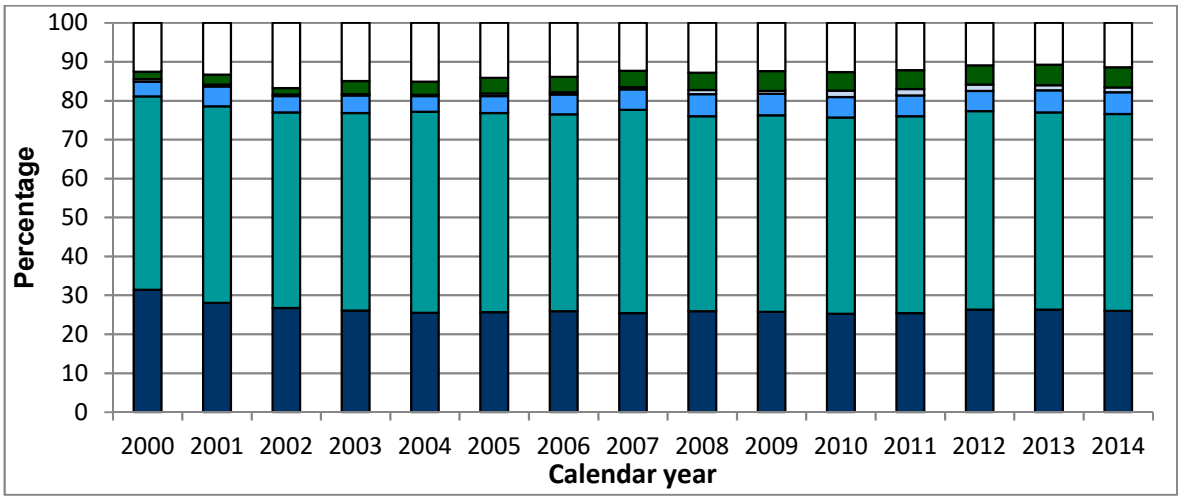
[a] Individuals could be included at more than one time point; [b] denominators are provided in column one of Table 5.1; [c] the mid-point of the boxes represent the median age in that year at the time of CD4 count or VL measurement, the ends of the boxes represent the upper and lower quartiles, and the lines represent the range.

Figure 5.2: Ethnicity among all individuals attending for care by gender/sexual orientation 2000-14

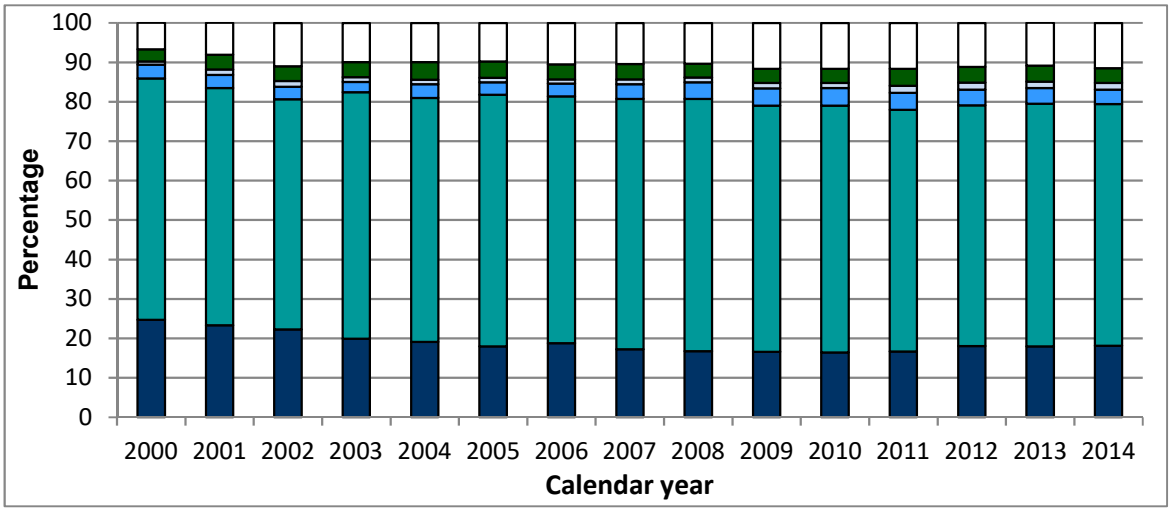
a): MSM [a b]



b): MSW



c): Women



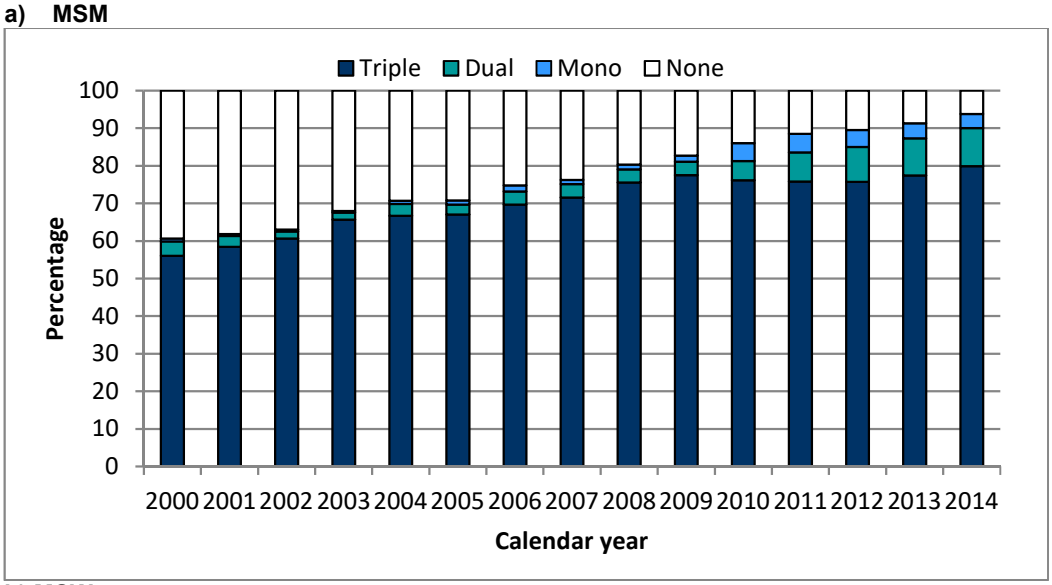
[a] Individuals could be included at more than one time point; [b] denominators are provided in column one of Table 5.1.

5.4.1.2 ***ART use***

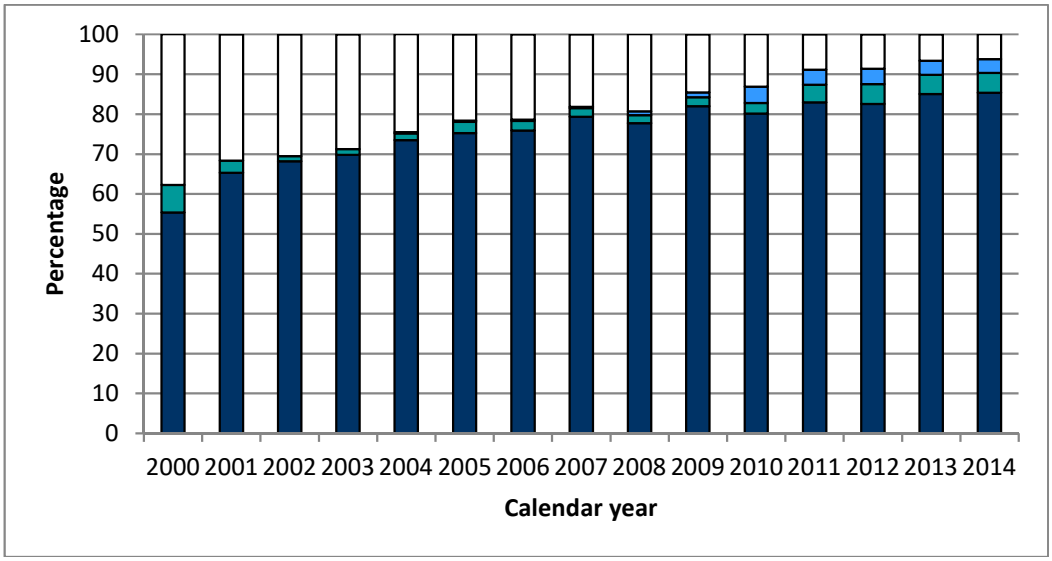
The proportion not on treatment decreased substantially over time from over 35% to less than 10% in all groups in 2014 (Figure 5.3a-c). Generally, a slightly lower proportion of women were on treatment compared to the male groups throughout the study period. Most individuals in each group were on triple ARV regimens (i.e. cART), although there has been a slight increase in mono and dual PI-based therapy in recent years.

Figure 5.3: Type of ART regimen received among all individuals attending for care by gender/sexual orientation 2000-14 [a] [b]

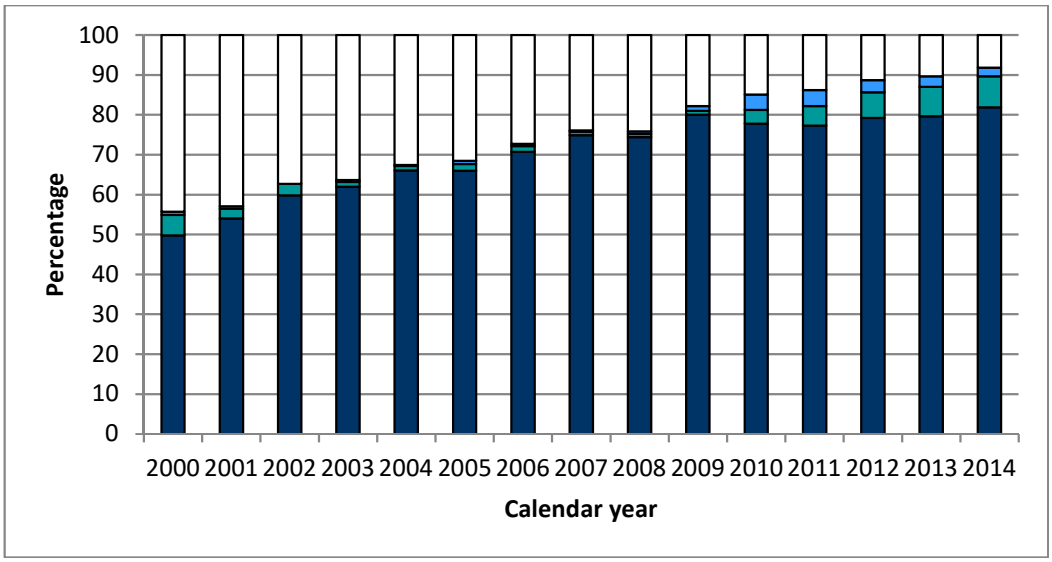
a) MSM



b) MSW



c) Women



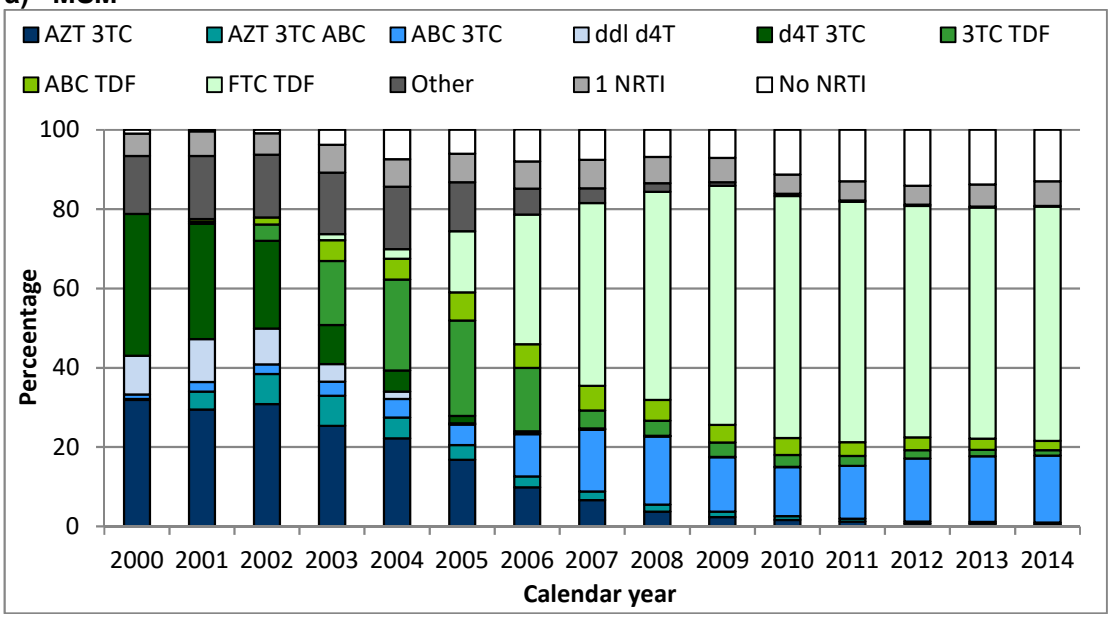
[a] Individuals could be included at more than one time point; [b] denominators are provided in column one of Table 5.1; mono= 1 ARV; double= 2 ARVs; triple= ≥3 ARVs (cART).

The specific ARVs used changed over time, in line with the introduction of new drugs and increased knowledge of the most effective regimens (Figures 5.4 and 5.5). Guidelines of which ARVs should be prescribed to PLWH changed over time and influenced which NRTI backbone and combination of ARV classes were used[50;133;134;136;137;142].

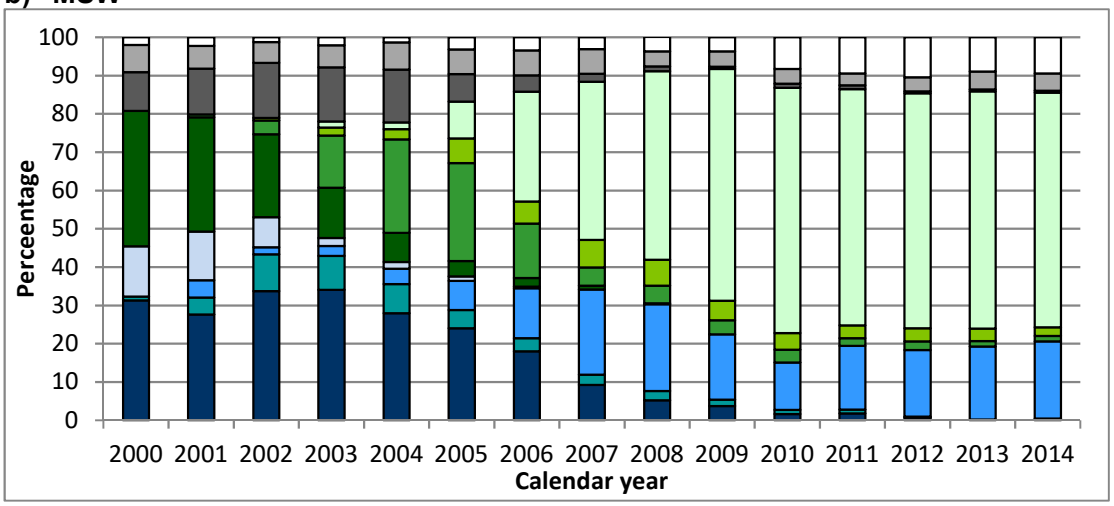
The NRTIs used over calendar time are displayed in Figure 5.4a-c. Across all three groups there has been a move away from regimens including AZT, ddI, and d4T, since these are no longer recommended at least for first-line treatment in the UK[73], towards TDF and FTC, which is now the preferred NRTI backbone. MSW and women were more likely to be using regimens including AZT than MSM in the earlier years. Also in the early 2000s, a greater proportion of the male groups were on d4T and 3TC compared to women. In the most recent years, the NRTIs used were similar for all three groups.

Figure 5.4: ART regimen NRTI backbone among all individuals attending for care and on ≥1 ARV by gender/sexual orientation 2000-14 [a] [b]

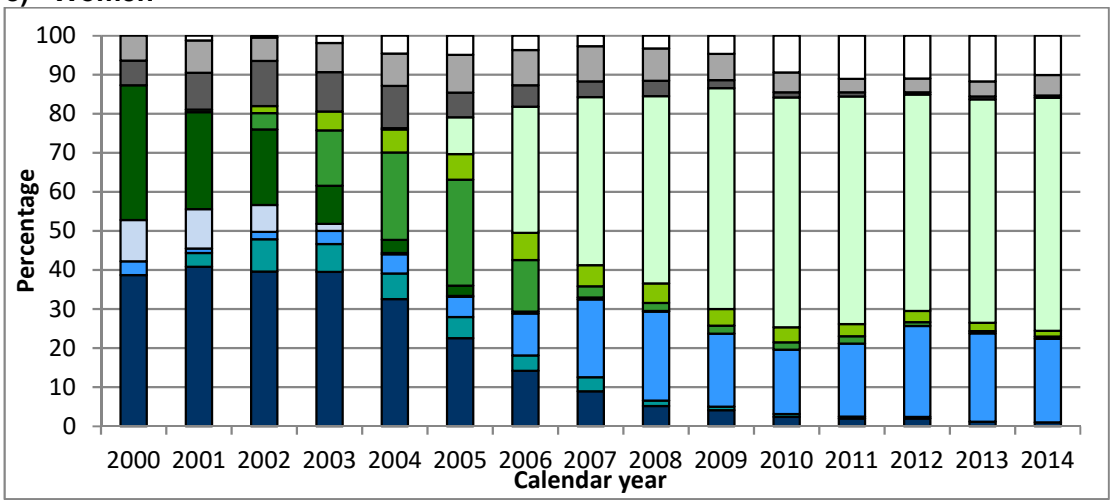
a) MSM



b) MSW



c) Women

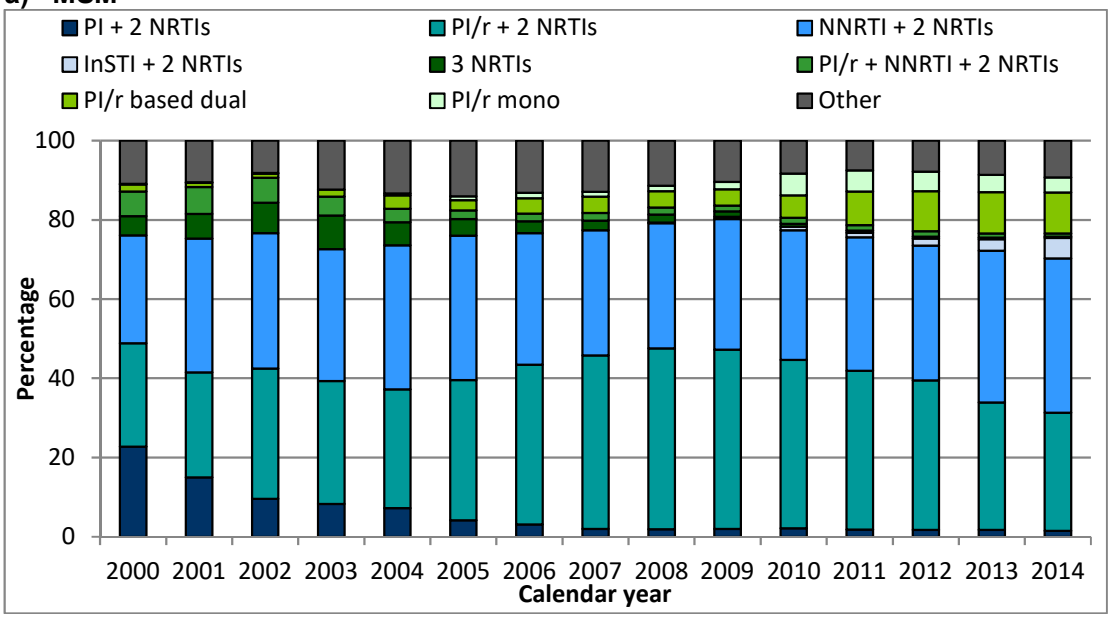


[a] Individuals could be included at more than one time point; [b] denominators are provided in column one of Table 5.1; NRTI=Nucleoside reverse transcriptase inhibitors; FTC= emtricitabine; TDF= tenofovir; ABC= abacavir; 3TC= lamivudine; d4T= stavudine; ddl= didanosine; AZT= zidovudine.

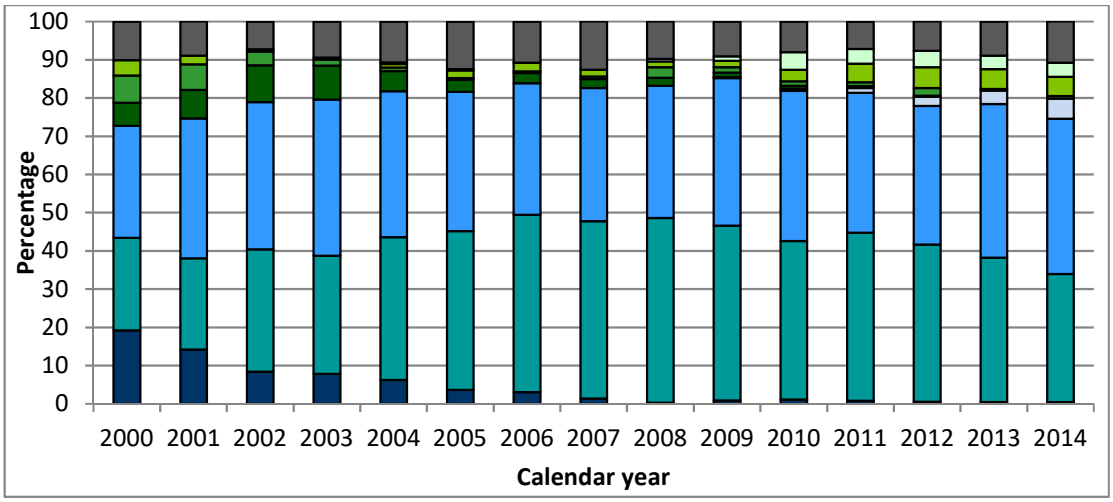
Trends over time in the distribution of ARV classes used are displayed in Figure 5.5a-c. Most individuals were on two NRTIs with either a ritonavir boosted Protease Inhibitor (PI) or Non-Nucleoside Reverse Transcriptase Inhibitor (NNRTI) for all gender/sexual orientation groups over all calendar years (i.e. PI-based or NNRTI-based cART). Before 2004, a lower proportion of women were on a PI-based cART and a higher proportion on an NNRTI-based cART compared to both male groups. Integrase Strand Transfer Inhibitors (InSTIs) were increasingly used in all three groups over calendar time, but use of InSTI-based cART only reached 5% in each group in 2014. There was an increase in PI-based dual and mono therapy from around 2009 onward, particularly among MSM. In this period, of the individuals on mono therapy, 92-100% were on a single PI, and, of those on dual therapy, 87-97% were on a PI-based regimen with an NNRTI, maraviroc, an InSTI, or an NRTI. The increase in prevalence of these regimens in recent years is likely a result of evidence of reasonable outcomes of mono and dual therapy regimens for individuals who have achieved initial VL suppression[67;72;565].

Figure 5.5: Distribution of ARV classes in regimen among all attending for care and on ≥1 ARV by gender/sexual orientation 2000-14 [a] [b]

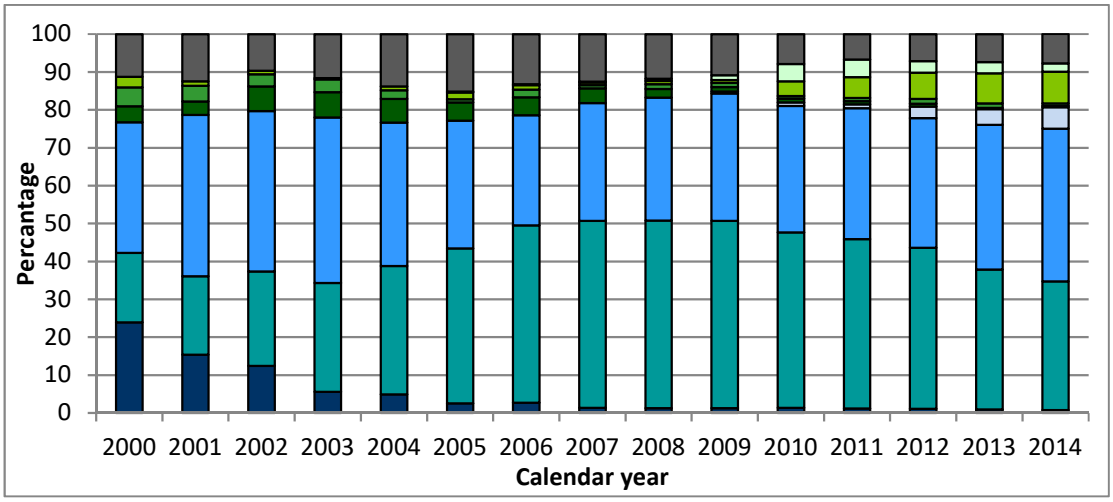
a) MSM



b) MSW



c) Women



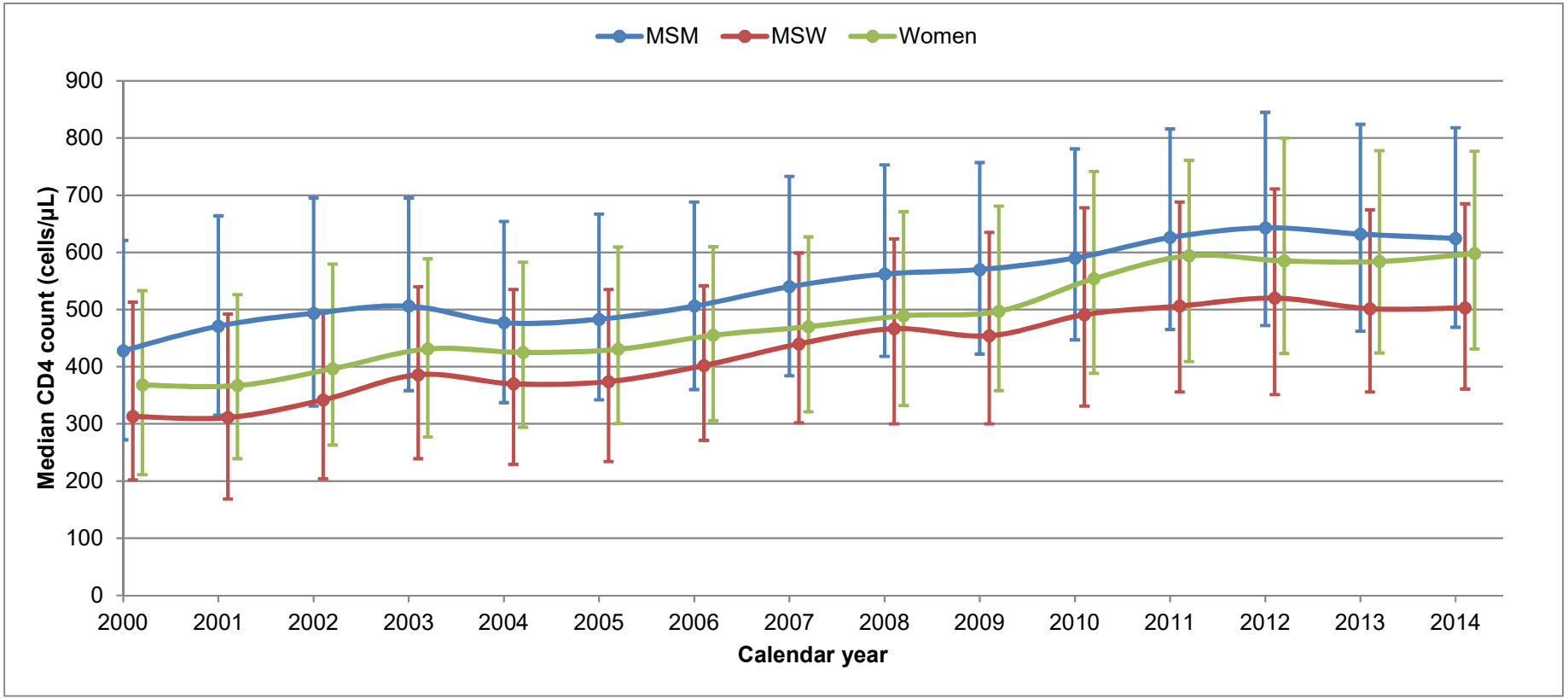
[a] Individuals could be included at more than one time point; [b] denominators are provided in column one of Table 5.1; PI= Protease inhibitor; NRTI=Nucleoside reverse transcriptase inhibitors; PI/r= ritonavir boosted PI; NNRTI= Non-Nucleoside reverse transcriptase inhibitor; InSTI= Integrase strand transfer inhibitor.

5.4.1.3 ***CD4 count***

Figure 5.6 displays the median and IQR for CD4 count over calendar year by gender/sexual orientation amongst all individuals under care. The points for each gender/sexual orientation group in this figure (and any subsequent scatter plot) are plotted at a slight offset on the x-axis so that it is visually clear. It can be seen that median CD4 count increased over calendar time for all groups, but that MSW consistently had the lowest value across all calendar years, followed by women, and then MSM. In 2014, compared to 2000, the median CD4 count was 197 cells/μL higher for MSM and 190 cells/μL higher for MSW. Women had the greatest difference of 230 cells/μL.

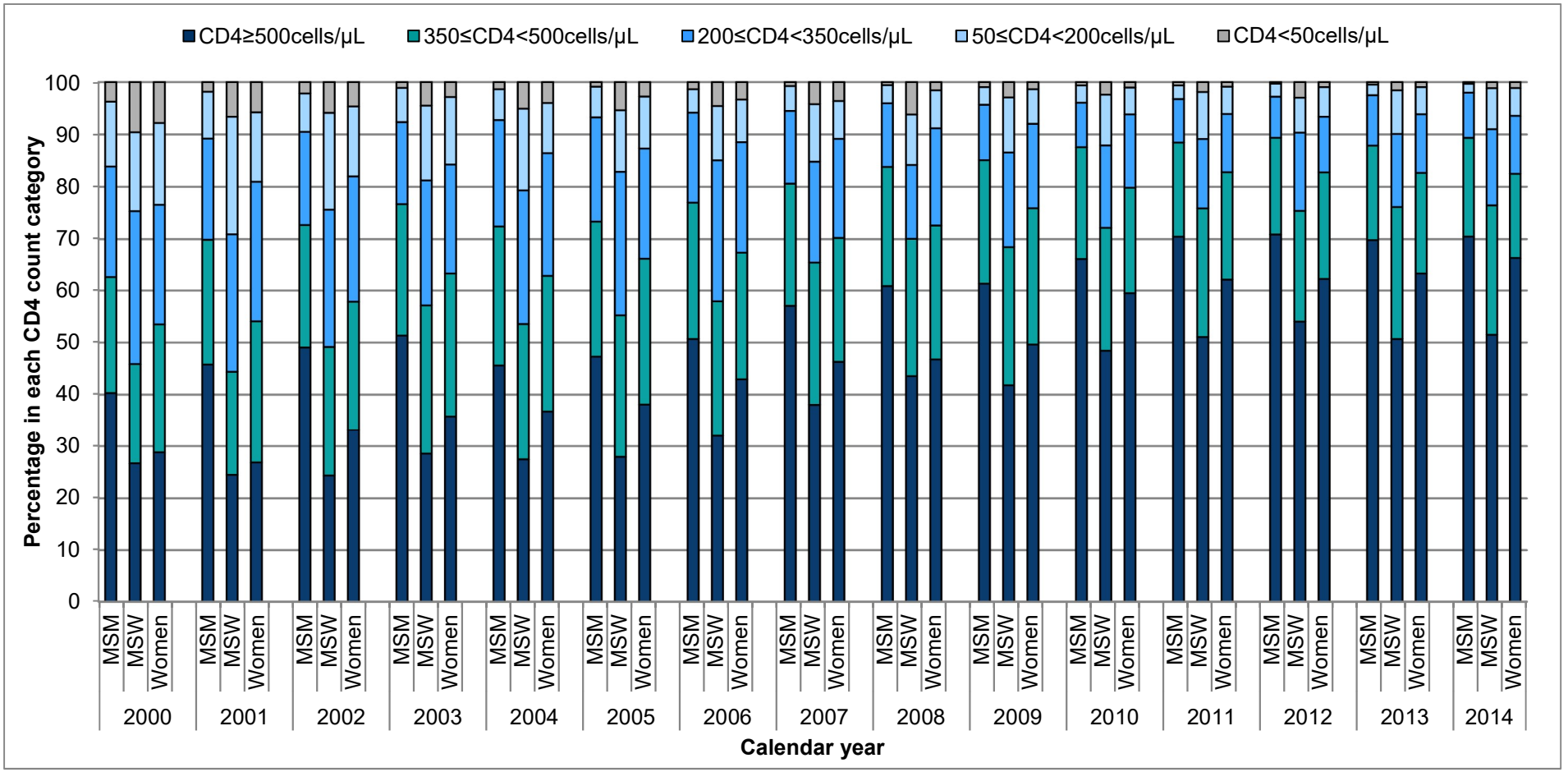
Over time, the percent with a CD4 count ≥500 cells/μL increased in all three gender/sexual orientation groups but was consistently highest among MSM (Figure 5.7). The prevalence of severe immunosuppression fell considerably over time. In 2000, 16% MSM, 25% MSW and 23% of women had CD4 counts <200 cells/μL. In 2014, these percentages had fallen to 2%, 9% and 6%, respectively.

Figure 5.6: Median (IQR) CD4 count among all individuals attending for care by gender/sexual orientation 2000-14 [a b c]



[a] Individuals could be included at more than one time point; [b] denominators are provided in column one of Table 5.1; [c] the bars around the median represent the IQR.

Figure 5.7: Distribution of current CD4 count among all individuals attending for care by gender/sexual orientation 2000-14 [a] [b]

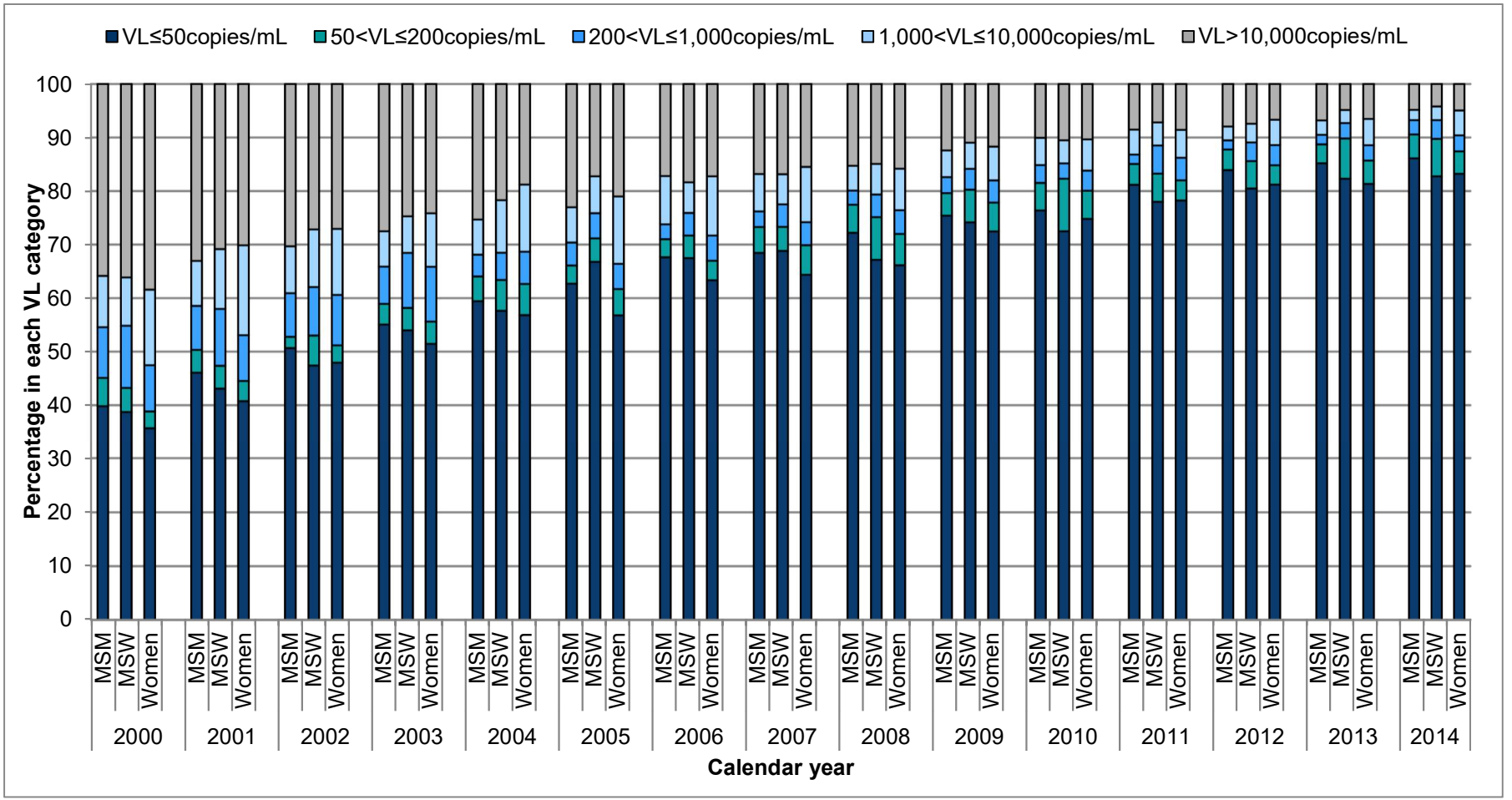


[a] Individuals could be included at more than one time point; [b] denominators for this graph are in column one of Table 5.1.

5.4.1.4 ***Viral load***

Over time, the proportion of the individuals attending for care who had a VL ≤50 copies/mL increased substantially in all three gender/sexual orientation groups (Figure 5.8). Likewise, the proportion with a VL >10000 copies/mL substantially declined. When looking at the differences between gender/sexual orientation groups, there have consistently been lower proportions of MSW and women with VL ≤50 copies/mL compared to MSM over the 15-year period. In 2014, 86% of MSM, 83% of MSW, and 83% of women in the complete clinic population had VL ≤50 copies/mL. Trends in VL non-suppression among people on cART was considered in Section 5.4.2.

Figure 5.8: VL among all individuals attending for care by gender/sexual orientation 2000-14 [a] [b]



[a] Individuals could be included at more than one time point; [b] denominators for this graph are in column one of Table 5.1.

5.4.1.5 *Rates of hospitalisation, AIDS, and death*

The total number of hospitalisations, AIDS events, and deaths and the total person-years of follow-up by gender/sexual orientation are shown in Table 5.2. The rates of hospitalisations, AIDS events and death have substantially decreased over time in all gender/sexual orientation groups, as seen in Figure 5.9a-c.

Throughout the follow-up period, MSW and women had a higher rate of hospitalisations compared to MSM. The differences in hospitalisations between MSM and the heterosexual groups were consistent between 2000 and 2014, as seen by the similar slopes for each group (Figure 5.9a), with the exception of 2012 where the rates of hospitalisation in MSM and MSW intersected. In 2014, these were 1.2, 3.5, and 2.9 per 100 person-years among MSM, MSW, and women, respectively.

Although MSW and women consistently had a higher rate of new AIDS events compared to MSW over the study period (Figure 5.9b). In 2000, the rate of AIDS among MSM was 4.3 per 100 person-years, declining to 0.6 in 2014. Similar declines were seen for MSW (8.4 to 1.8) and women (5.9 to 1.0).

Figure 5.9c shows that, although the death rate has decreased among all groups over the 15-year period it did so to a lesser extent compared to AIDS events and hospitalisation. One would expect that the rate of death among women would be consistently below that of both male groups, reflecting the pattern seen in the general population[566]. This should particularly be the case since women attending the ICDC had a lower median age than the male groups. However, the rates of death among women were only below those of MSW and not MSM. In 2000, the rate of death was 1.8, 4.4, and 1.9 per 100 person-years for MSM, MSW, and women, respectively. Over time, the rates among MSW approached those of MSM and women, and in 2010 the death rate in MSW had declined to 0.7 per 100 person-years, and thus reached the low rates seen among MSM. In 2014 the rates of death were 1.1, 0.9, and 0.1 for MSM, MSW, and women.

When hospitalisation or AIDS events at presentation (within three months of first visit to the ICDC) were excluded, there were substantially reduced rates of these clinical events in all gender/sexual orientation groups (Figure 5.10a-b). Furthermore, the differences in the rates of these events by gender/sexual orientation were much reduced. However, death rates remained largely unchanged by the exclusion of deaths in the first three months (Figure 5.10c).

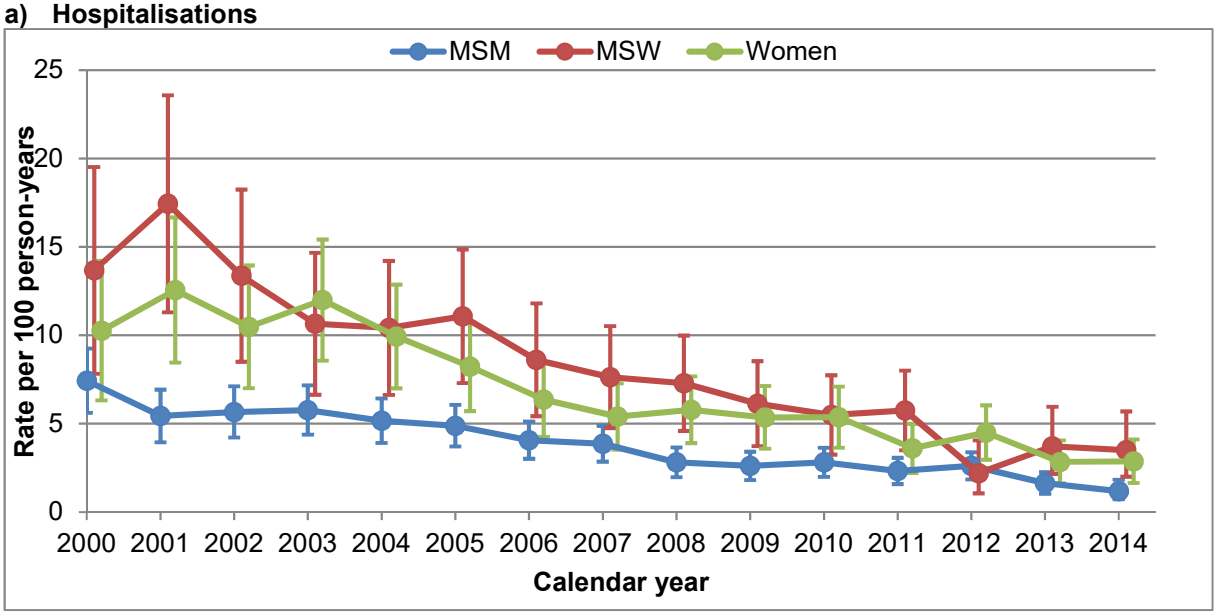
Table 5.2: Total years of follow-up and number of hospitalisations, AIDS events and death observed by gender/sexual orientation among individuals attending for care 2000-14

Year	Hospitalisations						AIDS events						Deaths					
	MSM		MSW		Women		MSM		MSW		Women		MSM		MSW		Women	
	PY	n	PY	N	PY	n	PY	n	PY	n	PY	n	PY	n	PY	n	PY	n
2000	861	64	154	21	253	26	862	37	155	13	255	15	881	16	160	7	262	5
2001	938	51	178	31	287	36	940	24	179	21	288	16	951	8	189	5	295	2
2002	1041	59	217	29	334	35	1042	37	219	17	335	28	1058	16	226	5	347	4
2003	1142	66	253	27	392	47	1144	35	254	14	396	25	1160	16	261	6	403	2
2004	1256	65	278	29	443	44	1257	26	279	18	445	35	1268	11	288	4	461	5
2005	1350	66	298	33	498	41	1350	25	299	20	502	19	1360	11	310	5	511	4
2006	1401	57	325	28	550	35	1403	26	326	21	554	22	1414	19	337	8	561	6
2007	1447	56	353	27	592	32	1449	22	355	16	593	12	1459	19	361	9	598	9
2008	1528	43	384	28	622	36	1529	18	386	20	625	18	1536	7	393	8	635	8
2009	1570	41	408	25	653	35	1572	20	408	13	656	14	1582	10	414	7	664	2
2010	1595	45	418	23	689	37	1598	15	420	7	694	8	1606	12	423	3	699	2
2011	1633	38	435	25	721	26	1637	13	437	12	721	9	1643	7	444	3	725	6
2012	1681	44	453	10	733	33	1683	10	454	7	733	18	1688	12	457	4	741	4
2013	1705	28	457	17	739	21	1706	10	458	8	739	9	1711	10	463	2	744	3
2014	1687	20	456	16	730	21	1687	10	457	8	732	7	1692	18	461	4	736	1
Total	20836	743	5066	369	8235	505	20858	328	5085	215	8266	255	21008	192	5185	80	8383	63

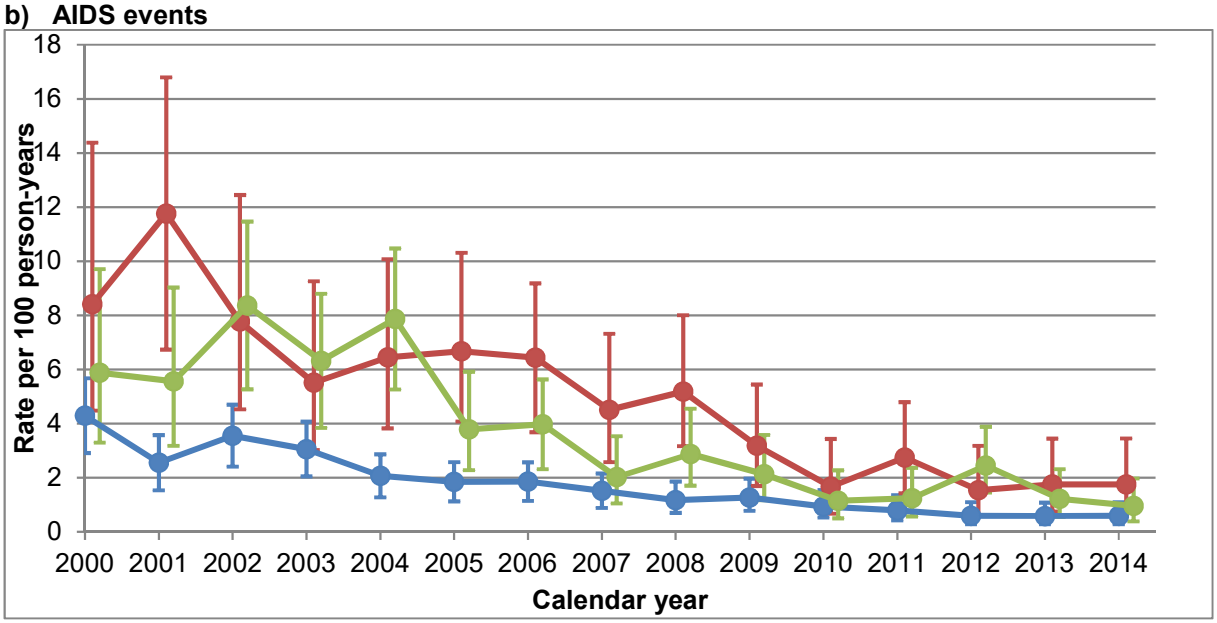
PY=person-years; n=number of events.

Figure 5.9: Rate [a] (95% CI) of clinical events over time by gender/sexual orientation

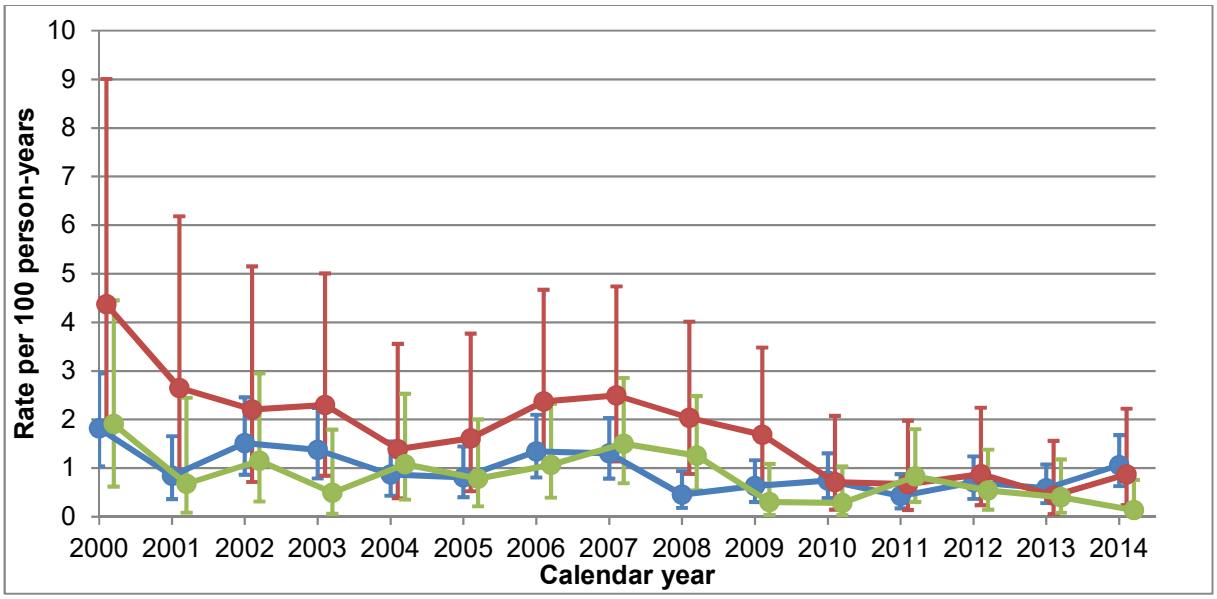
a) Hospitalisations



b) AIDS events



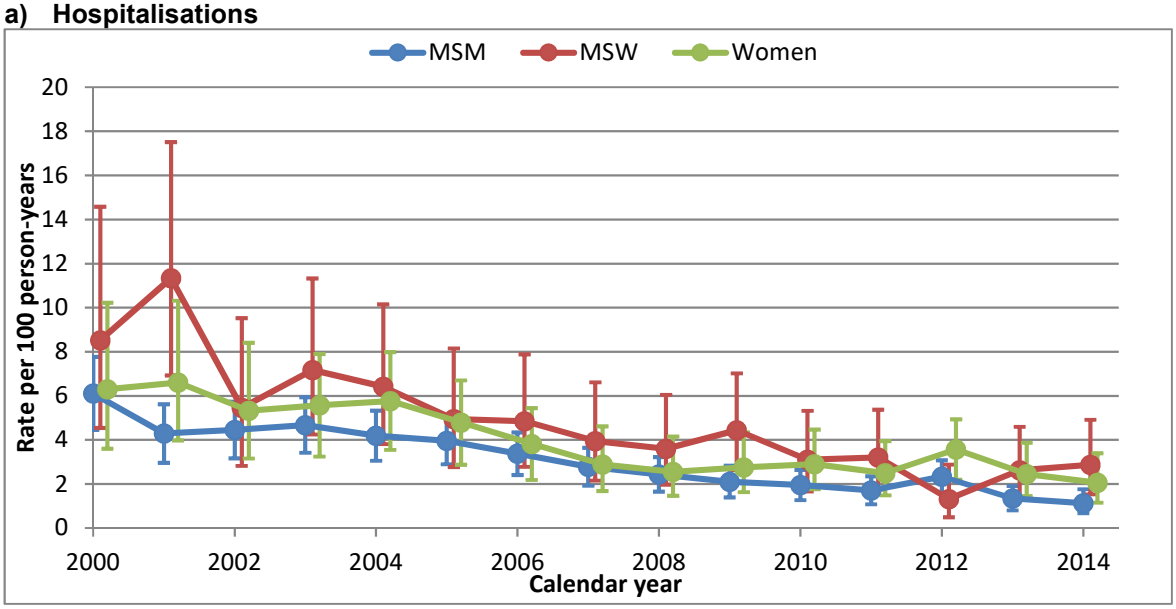
c) Death



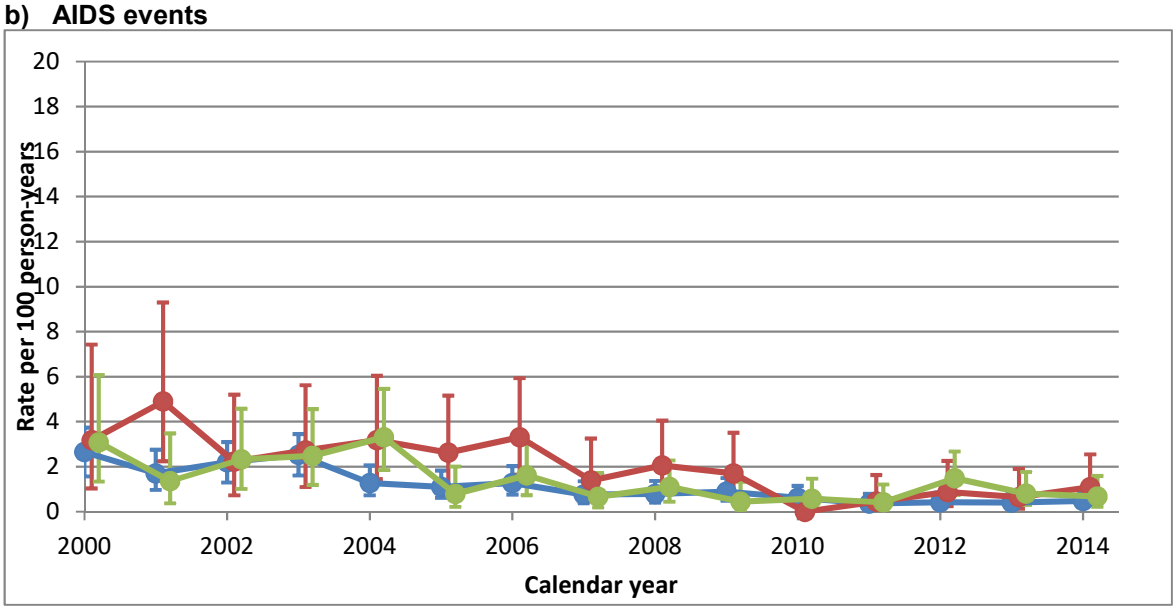
[a] Per 100 person-years; the bars on these graphs represent confidence intervals.

Figure 5.10: Rate [a] (95% CI) of clinical events over time by gender/sexual orientation excluding events within first three months of presentation to the Royal Free Hospital

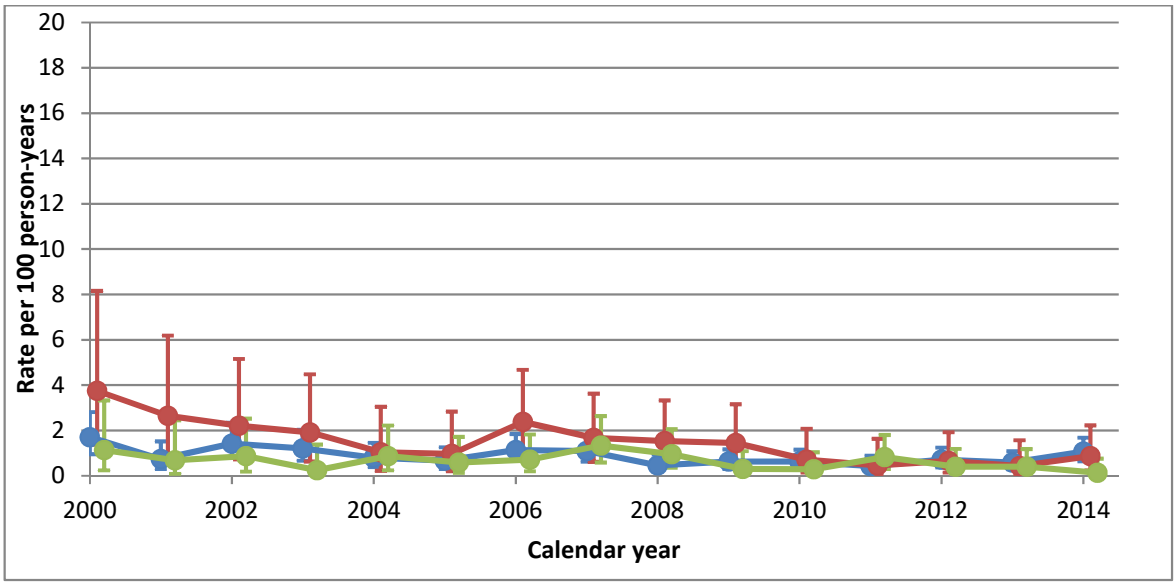
a) Hospitalisations



b) AIDS events



c) Death



[a] Per 100 person-years; the bars on these graphs represent confidence intervals.

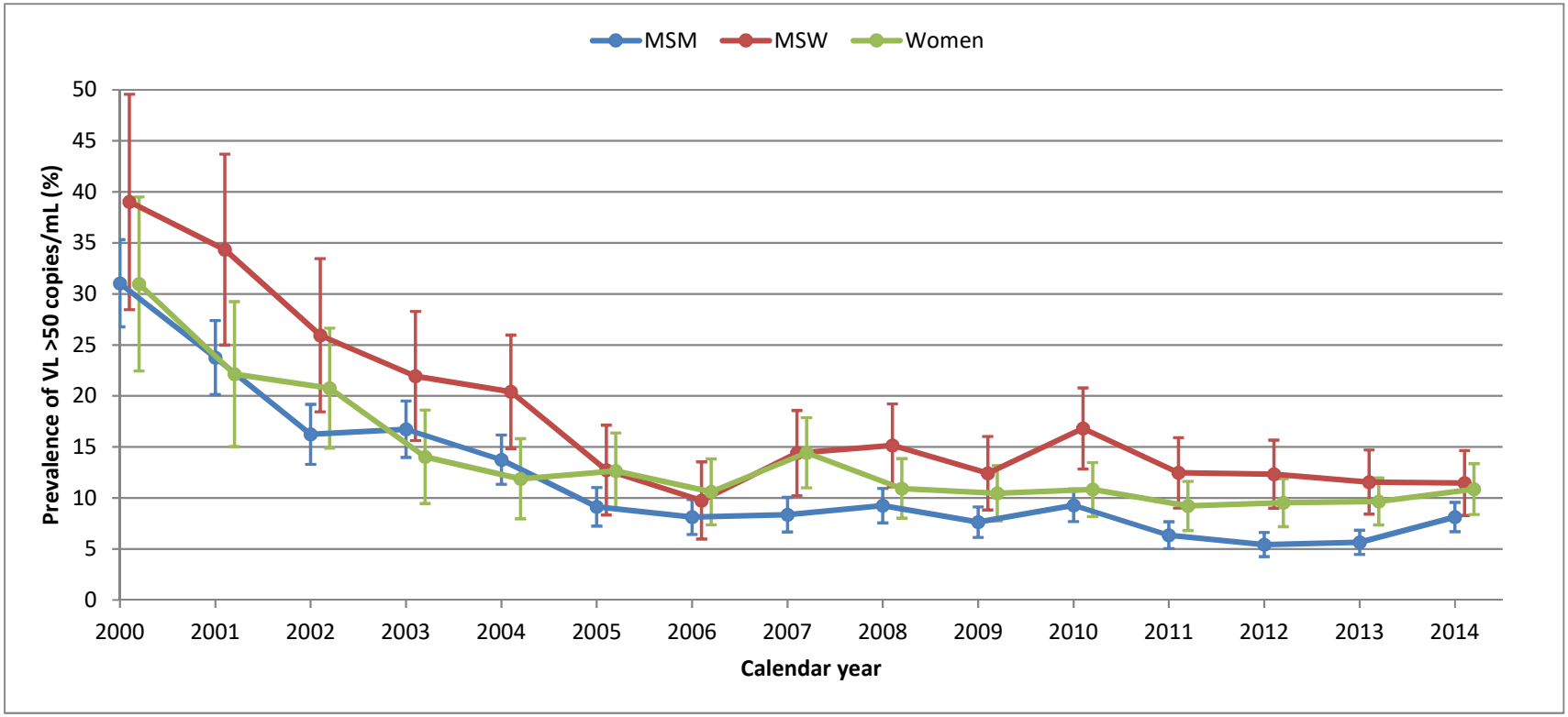
5.4.2 **Trends over time in prevalence of virological non-suppression**

5.4.2.1 ***VL among individuals currently receiving continuous cART for at least six months***

This section focuses on trends in virological non-suppression on cART. This first sub-section considers the sub-population described in Section 5.3.3, and focuses on individuals currently receiving continuous cART for at least 6 months at the time of the VL measurement. The second column of Table 5.1 shows the denominators used for these analyses.

As shown in Figure 5.11, the prevalence of virological non-suppression among individuals currently receiving continuous cART fell dramatically between 2000 and 2014. For all gender/sexual orientation groups, the decline appeared to occur predominantly between 2000 and 2006, with only a marginal decline subsequently. Among MSM, the prevalence of virological non-suppression fell from 31% in 2000 to just 8% in 2014. Likewise, among MSW and women, 39% and 31% had virological non-suppression in 2000, respectively, compared to 11% of each group in 2014. A greater percentage of MSW had virological non-suppression than MSM in all calendar years and a greater percentage of women had virological non-suppression than MSM from 2005 onward. Examining the figures visually, the pattern of the reduction in the prevalence of virological non-suppression over time (shown by the slope of the line) appeared similar in all gender/sexual orientation groups.

Figure 5.11: Prevalence of VL >50 copies/mL by gender/sexual orientation among individuals currently receiving continuous cART for at least six months 2000-14 [a] [b]



[a] Individuals could be included at more than one time point; [b] denominators are provided in column two of Table 5.1; the bars on graph represent confidence intervals.

The results presented in Figure 5.11 suggested a non-linear association between calendar time and virological non-suppression. Furthermore, when including a quadratic term for calendar year in the model, this was strongly associated with virological non-suppression ($p<0.0001$ in a model including calendar year and calendar year squared only) which provided further evidence of a non-linear effect.

Thus, as described in the methods section, I fitted a piecewise linear slope to investigate changes over calendar time in the prevalence of virological non-suppression. Using Figure 5.11, I decided to allow for a change in the slope at the year 2006. The results of the piecewise model demonstrated strong evidence for a change in slope in 2006: in 2006-14 the change in prevalence per year was 0.84 times that seen in 2000-06 (95% CI: 0.81, 0.87; $p<0.0001$). This corresponded to an 18% relative reduction in prevalence of virological non-suppression per year before 2006, and a 2% relative reduction in prevalence of virological non-suppression per year after 2006, in a model including only gender/sexual orientation and the two calendar year terms (Table 5.3). After adjustment for age and new patient status, there remained a strong downward trend in the prevalence of virological non-suppression per calendar year before 2006; however, after 2006 there was no evidence of a decline over time.

Table 5.3 also shows the associations between gender/sexual orientation and virological non-suppression. There were significant differences between each of the gender/sexual orientation groups. The prevalence ratio of 1.56 comparing MSW and MSM means that MSW had a 56% greater prevalence of virological non-suppression compared to MSM across the whole time-period. Similarly, women had 24% greater prevalence of virological non-suppression compared to MSM. In addition, there was evidence of a 19% lower prevalence of virological non-suppression among women compared to MSW. Following additional adjustment for age and new patient status, there remained evidence of differences between in prevalence of non-suppression between each of the gender/sexual orientation groups, with MSM having the most favourable profile and MSW the least favourable. Younger age and less than six months since an individual's first visit to the ICDC compared to >12 months were associated with a substantially higher prevalence of virological non-suppression.

Table 5.3: Association between gender/sexual orientation, calendar year and VL >50 copies/mL among individuals currently receiving continuous cART for at least six months [ab]

Covariates		Model including gender/sexual orientation and calendar year			Model additionally including age and new patient status		
		aPR	95% CI	P-value[c]	aPR	95% CI	P-value[c]
Gender/ sexual orientation	MSW vs. MSM	1.56	1.34, 1.81	<0.0001	1.59	1.37, 1.84	<0.0001
	Women vs. MSM	1.24	1.09, 1.44		1.18	1.03, 1.35	
	Women vs. MSW	0.81	0.68, 0.96		0.74	0.63, 0.88	
Calendar year 2000-06	Per year	0.82	0.80, 0.84	<0.0001	0.84	0.82, 0.86	<0.0001
Calendar year 2006-14	Per year	0.98	0.96, 1.00	0.045	1.00	0.98, 1.02	0.96
Age	Per 10 years	-	-	-	0.81	0.76, 0.86	<0.0001
New patient status (time since first visit to the ICDC)	≤6 months vs. >12 months	-	-	-	2.22	1.97, 2.50	<0.0001
	6-12 months vs. >12 months	-	-		1.12	0.95, 1.32	

[a] PRs compare the relative positions of the slopes for VL >50 copies/mL over time, a slope which is assumed to stay the same over the study period; [b] individuals could be included at more than one time point; [c] likelihood ratio test; aPR= adjusted Prevalence Ratio.

Test for interaction between gender/sexual orientation and calendar year

In all models fitted until now, I have assumed that all three gender/sexual orientation groups had the same change over calendar time in terms of the relative prevalence of virological non-suppression. This section investigates whether there were different slopes for each gender/sexual orientation group. In other words, I am assessed whether there were different relative changes over time in three groups, and therefore, whether or not the MSW and women were "catching up" or "falling behind" the MSM, by experiencing a faster or slower decline over time in the prevalence of virological non-suppression. This was achieved by a test for interaction between gender/sexual orientation and calendar year. As a result of the findings in the previous paragraph, calendar year was considered in the two periods: 2000-06 and 2006-14. The results are shown in Table 5.4. Recall that here I am considering the relative changes over time in virological non-suppression among the three groups. In the period 2000-06, MSM had an adjusted PR of 0.82, corresponding to an 18% reduction in the prevalence of virological non-suppression per year later. Among MSW and women, these figures were 15% and 13%, respectively. Thus there were greater relative improvements over time for MSM than the other two groups before 2006, but the

differences between the groups were not statistically significant (p=0.15; test for interaction). In contrast, there was no evidence of a change in the prevalence of virological non-suppression over time among MSM, MSW, or women between 2006 and 2014, nor that these changes over time were different between the three groups (p=0.58; test for interaction). In a model solely including the post-2006 period, similarly there was no evidence of differences between the gender/sexual orientation groups (p=0.62).

Table 5.4: Associations of the interaction between gender/sexual orientation and calendar year with virological non-suppression among individuals currently receiving continuous cART for at least six months [a]

		aPR [b]	95% CI	P-value for interaction [c]
Relative change per year later: 2000-06	MSM MSW Women	0.82 0.85 0.87	0.80, 0.85 0.80, 0.89 0.83, 0.92	0.15
Relative change per year later: 2006-14	MSM MSW Women	0.99 1.01 1.01	0.96, 1.02 0.97, 1.05 0.97, 1.04	0.58

[a] Individuals could be included at more than one time point; [b] adjusted for age and new patient status; [c] likelihood ratio test examining whether there is a difference in change over time between the three gender/sexual orientation groups; aPR= adjusted Prevalence Ratio.

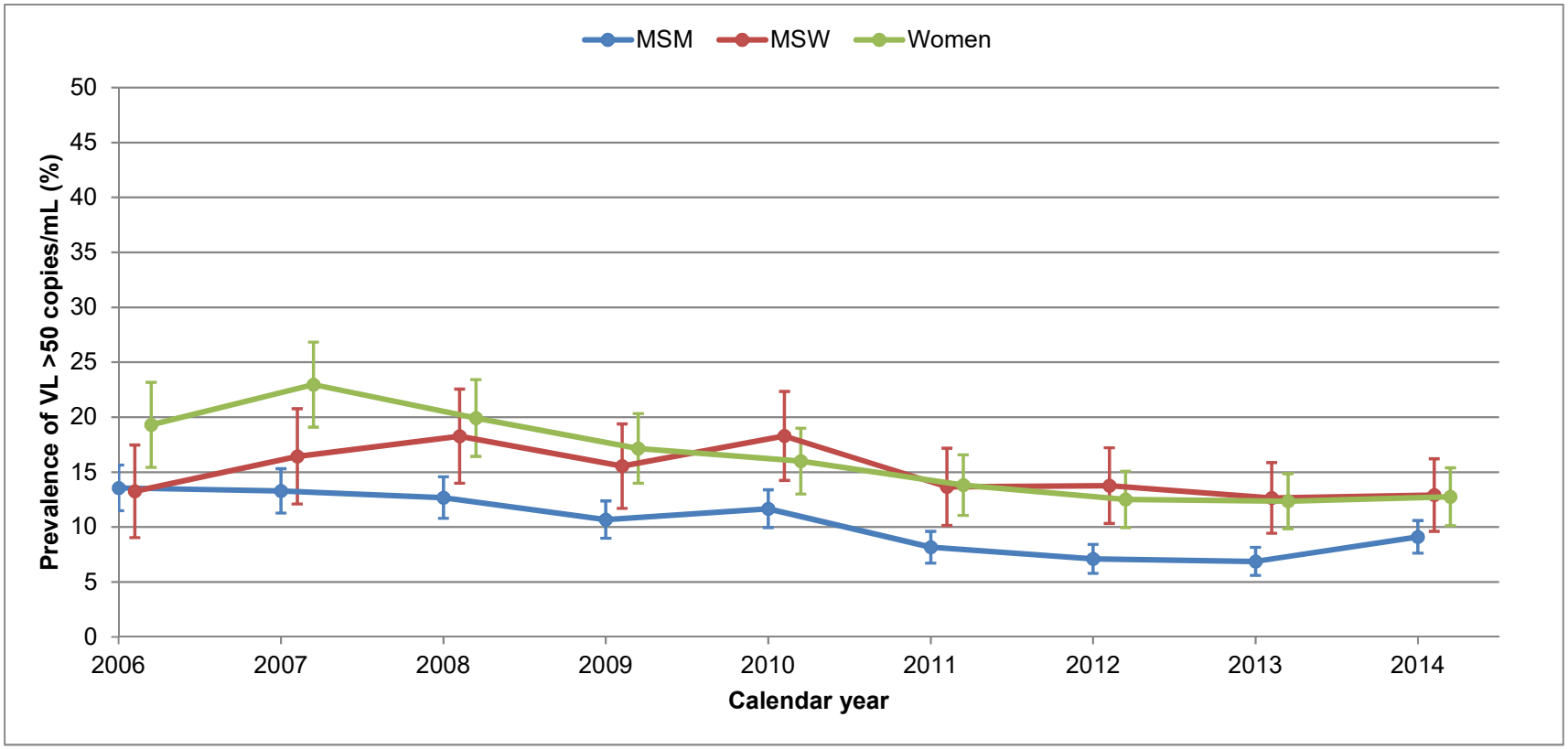
5.4.2.2 *VL among individuals who ever started cART*

This section considers the second sub-population described in Section 5.3.3of those that have ever started cART more than six months previously, regardless of whether they interrupted or currently remained on cART. The final column of Table 5.1 shows the denominators for the analyses in this section.

When considering this sub-population, as opposed to those on continuous ART for at least six months (Section 5.4.2.1), the prevalence of VL >50 copies/mL was between 1.5% and 7% higher in each year. The difference in prevalence of virological non-suppression found between these sub-populations decreased over the study period.

MSW and MSM have a comparable prevalence of virological non-suppression in 2006 (13% vs. 12% respectively), however, after this date the difference between the groups increased, with MSM having a lower prevalence (Figure 5.12). Women had an initially higher prevalence of virological non-suppression than MSM in 2006 (19% vs. 12% respectively), and this gap does not appear to have lessened over time, with substantial differences between these groups found in most years. MSW and women had a similar prevalence of virological non-suppression from 2008 onward, and in 2014, 13% of both groups had a VL >50 copies/mL compared to 9% of MSM.

Figure 5.12: Prevalence of VL >50 copies/mL by gender/sexual orientation among individuals ever on cART 2006-14 [a b]



[a] Individuals could be included at more than one time point; [b] denominators are provided in column three of Table 5.1; the bars on graph represent confidence intervals.

In this analysis, only considering 2006 onwards, there was no evidence of a non-linear trend between calendar year and VL non-suppression (p=0.72 in a model including calendar year and calendar year squared only), a finding which was corroborated by visual examination of Figure 5.12. Therefore, I considered calendar year as a continuous linear variable in subsequent analyses.

Table 5.5 shows the PRs for the associations of gender/sexual orientation and calendar year with virological non-suppression when assuming the same relative change over time in prevalence of non-suppression in all three gender/sexual orientation groups. In a model including gender/sexual orientation and calendar year only, there were higher prevalence's of virological non-suppression among MSW and women compared to MSM (by 43% and 57% respectively), but no evidence of differences between MSW and women. For each year later, there was a 6% lower prevalence of virological non-suppression on average. The effects of gender/sexual orientation and calendar year were marginally attenuated following additional adjustment for age and new patient status.

Table 5.5: Association between gender/sexual orientation, calendar year and VL >50 copies/mL among individuals ever on cART [a b]

Covariates		Model including gender/sexual orientation and calendar year			Model additionally adjusted for age and new patient status		
		aPR	95% CI	P-value[c]	aPR	95% CI	P-value[c]
Gender/ sexual orientation	MSW vs. MSM	1.43	1.20, 1.69	<0.0001	1.47	1.24, 1.73	<0.0001
	Women vs. MSM	1.57	1.36, 1.81		1.41	1.23, 1.62	
	Women vs. MSW	1.10	0.92, 1.32		0.96	0.80, 1.15	
Calendar year	Per year	0.94	0.93, 0.96	<0.0001	0.96	0.95, 0.98	<0.0001
Age	Per 10 years	-	-	-	0.72	0.68, 0.77	<0.0001
New patient status (time since first visit to the ICDC)	≤6 months vs. >12 months	-	-	-	1.71	1.47, 1.99	<0.0001
	6-12 months vs. >12 months	-	-		1.03	0.85, 1.25	

[a] PRs compare the relative positions of the slopes for VL >50 copies/mL over time, a slope which is assumed to stay the same over the study period; [b] individuals could be included at more than one time point; [c] likelihood ratio test; aPR= adjusted Prevalence Ratio.

Test for interaction between gender/sexual orientation and calendar year

There was weak evidence of different changes over time in the prevalence of non-suppression between gender/sexual orientation groups when adjusting for age and new patient status (p=0.066; test for interaction) (Table 5.6). Both MSM and women

had a 5% lower prevalence of virological non-suppression per year on average; however, there was no evidence of a reduction in the prevalence of virological non-suppression over calendar time among MSW. This may reflect the fact that overall prevalence of virological non-suppression in this latter group was particularly low at the start of the period under consideration, and as such could not decrease substantially further.

Table 5.6: Associations of the interaction between gender/sexual orientation and calendar year with virological non-suppression among individuals ever on cART [a]

		aPR [b]	95% CI	P-value[c]
Relative change per year later: 2006-14	MSM	0.95	0.93, 0.97	0.066
	MSW	1.00	0.96, 1.04	
	Women	0.95	0.93, 0.99	

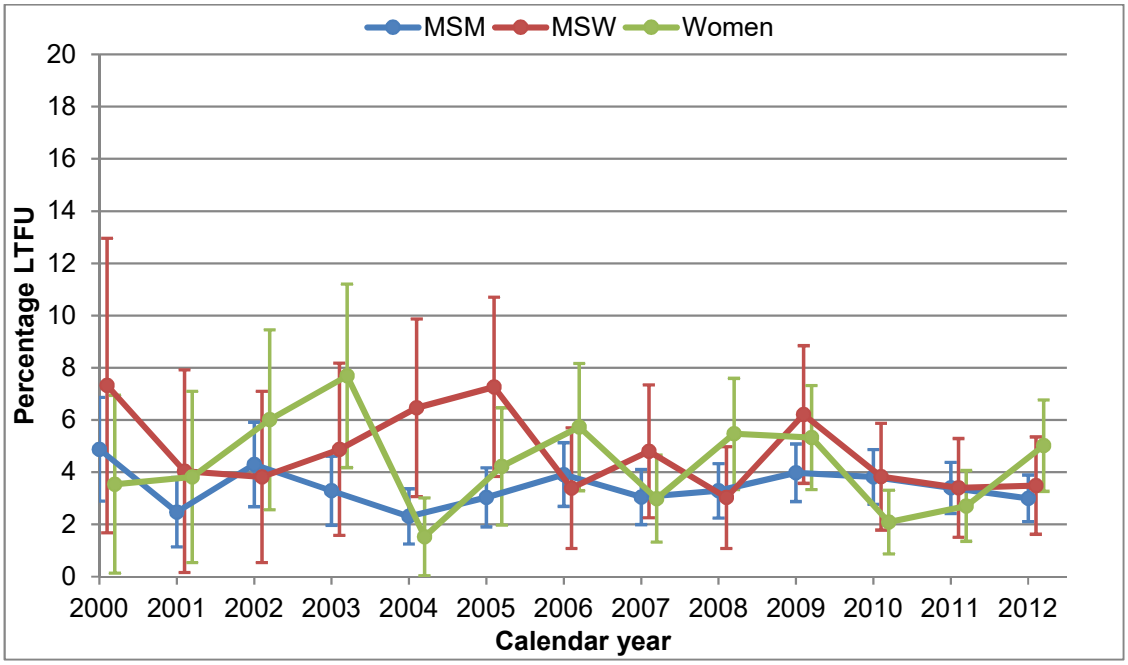
[a] Individuals could be included at more than one time point; [b] adjusted for age and new patient status; [c] likelihood ratio test; aPR= adjusted Prevalence Ratio.

5.4.3 **Loss to follow-up**

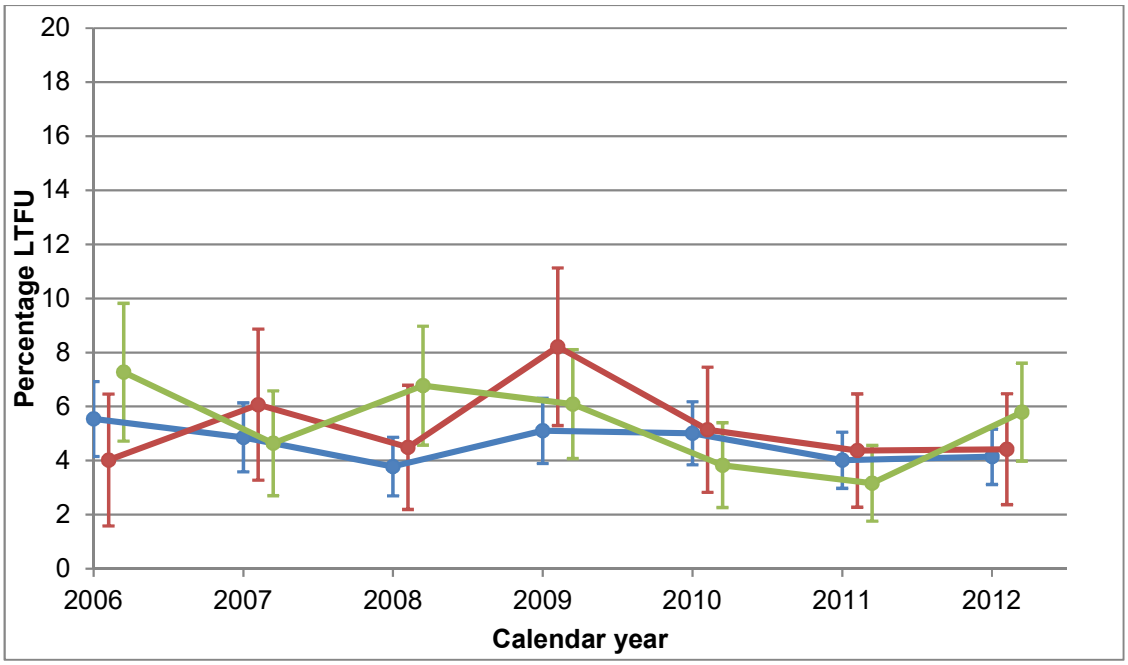
Next, I considered LTFU over time in the three gender/sexual orientation groups in both sub-populations used for the non-suppression analysis. For the sub-population who had received continuous cART for at least 6 months, the percentage of individuals LTFU in each year varied between 2% and 8%, with similar proportions in the three groups (Figure 5.13a). Likewise, among individuals who ever received cART there was a similar proportion of LTFU in all three gender/sexual orientation groups, so it is unlikely to have influenced the differences in virological non-suppression (Figure 5.13b).

Figure 5.13: Proportion lost to follow-up [a] by gender/sexual orientation 2000-12 [b]

a): Among individuals currently receiving continuous cART for at least six months [c]



b): Among individuals ever on cART [d]



[a] Lost to follow-up = no VL recorded in the subsequent two years; [b] individuals could be included at more than one time point; [c] denominators are provided in column two of Table 5.1; [d] denominators for this graph are in column three of Table 5.1.

5.4.4 **Sensitivity analyses**

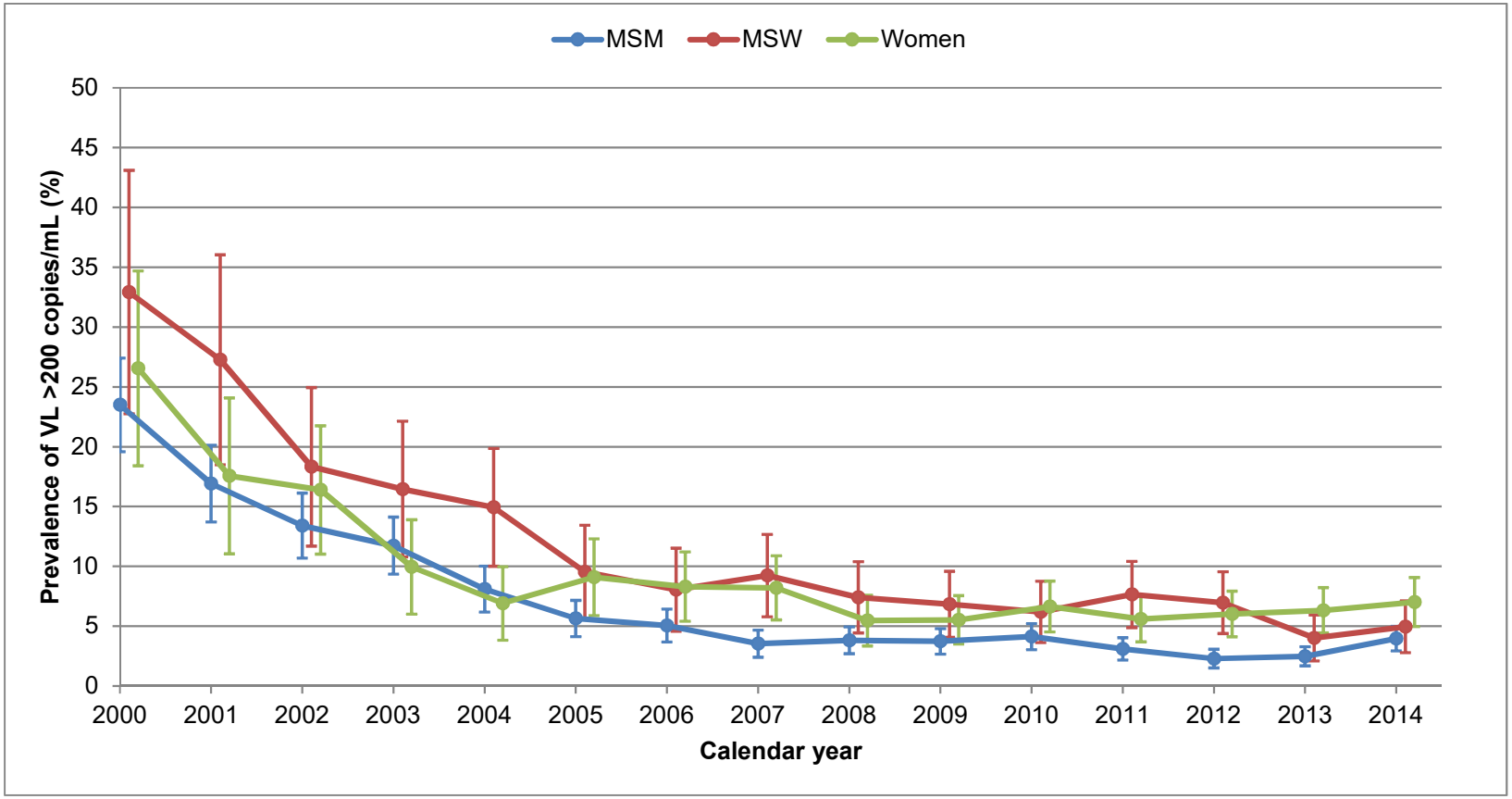
In a sensitivity analysis, virological non-suppression was re-defined as a VL measurement >200 copies/mL rather than >50 copies/mL. Figure 5.14 and Figure 5.15 show the prevalence of VL >200 copies/mL over time by gender/sexual orientation among the two sub-populations considered: individuals currently receiving continuous cART for at least six months and individuals who ever received cART, respectively. These results were similar to the main analysis with the exception that there still appeared to be a reduction in the prevalence of virological non-suppression post-2006 in the currently receiving cART sub-population, which was not the case in the main analysis.

Similar to the main analyses, there was evidence of a change in slope at 2006 in the analysis of individuals currently receiving continuous cART (PR=0.81 per year later 2006-14 vs. per year later 2000-06; 95% CI: 0.77, 0.86; p<0.0001), so a piecewise regression model was used. There was no evidence of a non-linear association with calendar year in the analysis of individuals who ever started cART (p=0.29), so calendar year could again be assessed as a single continuous variable.

Table 5.7 shows adjusted PRs for the association of gender/sexual orientation, calendar year, age, and new patient status with virological non-suppression under both of these analysis strategies. The results of the sensitivity analyses were similar to those of the main analyses, although the effect sizes were generally greater in the former.

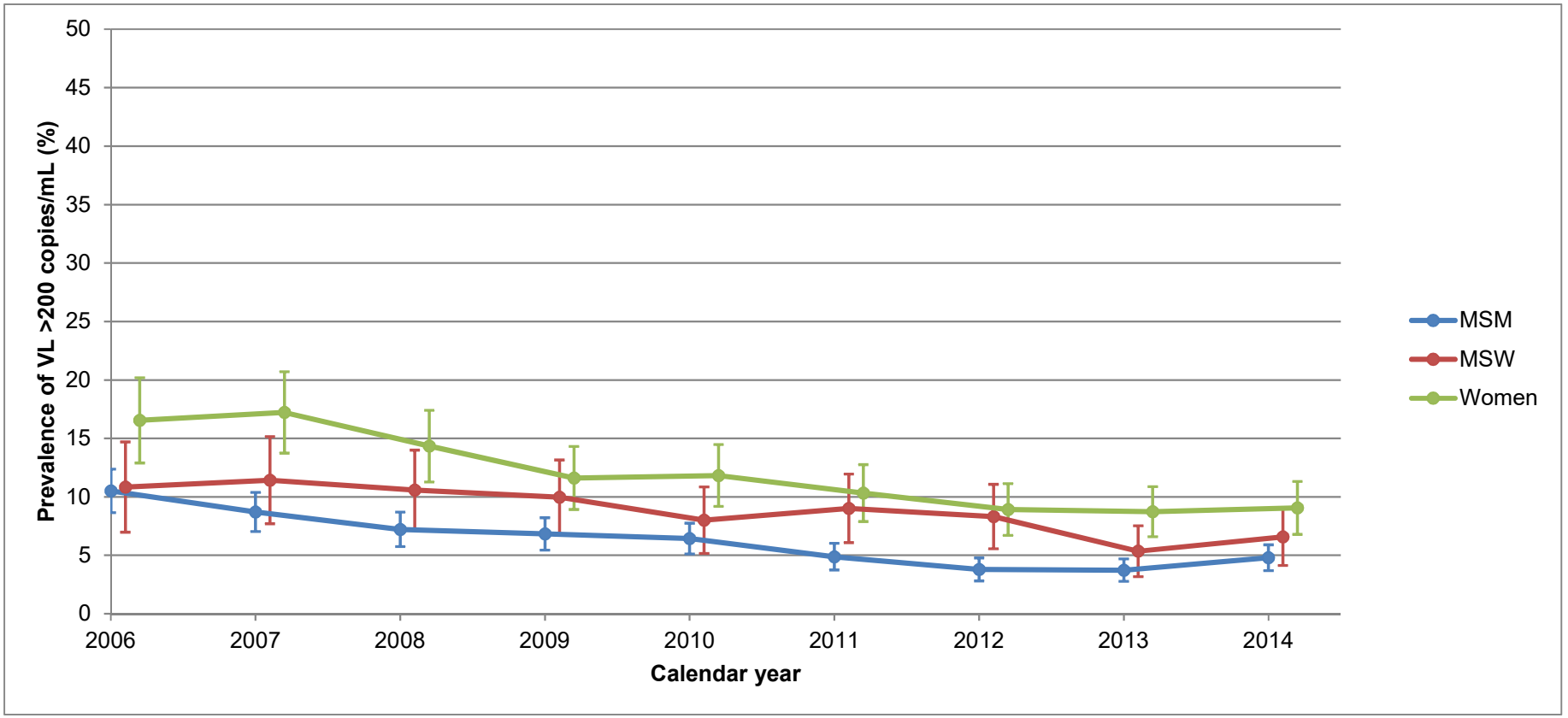
The results for tests for interaction between gender/sexual orientation and calendar time for both analysis strategies are shown in Table 5.8. These were consistent with the main analyses.

Figure 5.14: Prevalence of VL >200 copies/mL by gender/sexual orientation among individuals currently receiving continuous cART for at least six months 2000-14 [a] [b]



[a] Individuals could be included at more than one time point; [b] denominators for this graph are in column two of Table 5.1; the bars on graph represent confidence intervals.

Figure 5.15: Prevalence of VL >200 copies/mL by gender/sexual orientation among individuals ever on cART 2006-14 [a] [b]



[a] Individuals could be included at more than one time point; [b] denominators for this graph are in column three of Table 5.1; the bars on graph represent confidence intervals.

Table 5.7: Association between gender/sexual orientation, calendar year and VL >200 copies/mL [a]

Covariates		Individuals currently receiving cART			Individuals ever started cART		
		aPR [b]	95% CI	P-value[c]	aPR [b]	95% CI	P-value[c]
Gender/ sexual orientation	MSW vs. MSM	1.67	1.38, 2.03	<.0001	1.41	1.12, 1.77	<.0001
	Women vs. MSM	1.38	1.17, 1.63		1.70	1.44, 2.01	
	Women vs. MSW	0.83	0.66, 1.03		1.20	0.96, 1.52	
Calendar year 2000-06	Per year	0.79	0.77, 0.82	<.0001	-	-	-
Calendar year 2006-14	Per year	0.98	0.95, 1.01	0.16	0.94	0.92, 0.96	<.0001
Age	Per 10 years	0.78	0.72, 0.84	<.0001	0.67	0.62, 0.73	<.0001
New patient status (time since first visit to the ICDC)	≤6 months vs. >12 months	2.74	2.36, 3.19	<.0001	1.91	1.58, 2.31	<.0001
	6-12 months vs. >12 months	1.07	0.86, 1.33		0.91	0.70, 1.16	

[a] Individuals could be included at more than one time point; [b] model includes gender/sexual orientation, calendar year, age, and new patient status; [c] likelihood ratio test; aPR= adjusted Prevalence Ratio.

Table 5.8: Associations of the interaction between gender/sexual orientation and calendar year with VL >200 copies/mL [a]

		Individuals currently receiving cART			Individuals ever started cART		
		aPR [b]	95% CI	P-value[c]	aPR [b]	95% CI	P-value[c]
Relative change per year later: 2000-06	MSM	0.77	0.74, 0.81	0.13	-	-	-
	MSW	0.82	0.77, 0.87		-	-	
	Women	0.82	0.77, 0.88		-	-	
Relative change per year later: 2006-14	MSM	0.97	0.93, 1.01	0.17	0.91	0.89, 0.94	0.14
	MSW	0.95	0.91, 1.01		0.96	0.91, 1.01	
	Women	1.02	0.97, 1.07		0.95	0.92, 0.98	

[a] Individuals could be included at more than one time point; [b] adjusted for age and new patient status; [c] likelihood ratio test; aPR= adjusted Prevalence Ratio.

5.5 **Discussion**

5.5.1 **Summary of results**

- The demographic composition of the Royal Free HIV cohort changed considerably between 2000 and 2014, reflecting the changes seen in the UK[543]. In particular, MSW and women constitute an increasing proportion of the cohort.
- Across all three gender/sexual orientation groups, there was a decreasing proportion of individuals of white ethnicity and an increase in median age. In terms of ARVs used, the gender/sexual orientation groups were generally similar. Considerable increases in the proportion receiving cART were observed over time and corresponding decreases in the proportion not on treatment (over 90% in all groups were receiving some form of ART by 2014).
- CD4 count <200 cells/μL and VL >10000 copies/mL were more prevalent for MSW and women compared to MSM in most years. However, the prevalence of these outcomes decreased considerably in all three groups over time. Similarly, the occurrence of clinical events, as measured by the rate of hospitalisations, AIDS and death, greatly decreased over time, such that the rates of these outcomes are low among all three gender/sexual orientation groups.
- Among cART-treated individuals under care between 2000 and 2014, there were substantial declines in the prevalence of virological non-suppression. Current treatment is now so successful that, amongst those who remain in care, only 9% of individuals currently receiving continuous cART, and 11% of individuals who have ever started cART had a VL >50 copies/mL in 2014. However, a greater percentage of MSW and women had virological non-suppression than MSM in most years.
- There was no evidence that the gender/sexual orientation differences in virological non-suppression narrowed in relative terms over time. In fact, while there were declines in the prevalence of virological non-suppression over time among MSM and women who had ever started cART, there was no evidence of declines among MSW. Therefore, if anything, the differences between MSM and MSW tended to widen slightly in relative terms over time since 2006.

5.5.2 **Interpretation of results**

The aging population observed in the present analysis, across all gender/sexual orientation groups, was likely primarily a result of the success of cART and consequent increases in life expectancy for people living with HIV[57;98] (as seen by the

lower rates of death over calendar time in Section 5.4.1.5). Moreover, there have been increases in diagnosis of HIV among older individuals over time[567]. In terms of the decreasing proportion of individuals of white ethnicity over time in the present study, this was primarily owing to the observed increase in prevalence of unknown ethnicity status. It was unlikely a result of an increase in individuals of non-white ethnicity, since in recent years the prevalence of new diagnoses among migrants and black-African individuals has been falling in Europe[543;568].

There was little difference between the gender/sexual orientation groups in terms of specific NRTI backbones and ARV classes used. This suggests that differences in ART regimen are unlikely to explain gender/sexual orientation differences observed in virological non-suppression. There was lower PI-use (boosted or un-boosted) among women between 2000 and 2004, but usage of this class was similar between gender/sexual orientation groups after this time.

Across the study population, 70% MSM, 52% MSW and 66% women had a CD4 count above the lower limit of the normal range (i.e. above 500 cells/μL) by 2014, indicating that the majority of individuals in all three groups were generally in good overall health with respect to their immunological status by this time. Although the majority of individuals had a CD4 count that would be considered to be in the 'normal range', there are data which show that a higher CD4 count is associated with lower risk of AIDS and death even among individuals with a CD4 count >500 cells/μL[569]. Since CD4 count was analysed among all individual attending the ICDC, regardless of time since HIV diagnosis or whether they had been ART-treated, the lower CD4 counts in the heterosexual groups could reflect later HIV diagnosis, delays in ART initiation, or poorer CD4 count reconstitution following ART initiation.

Improvements in virological suppression from 2000 to 2014 at the entire clinic population level were likely reflective primarily of the corresponding increases in prevalence of ART use (Section 5.4.1.2). Additionally there were substantial changes in the NRTI regimen backbones used over time away from AZT, ddI and d4T towards FTC and TDF[476]. Use of more efficacious ARVs and ones that can be taken in a single combined tablet may also have contributed to the improvements in virological status over time.

Hospitalisation and AIDS rates were higher among MSW and women compared to MSM. When individuals hospitalised or with AIDS events at presentation were excluded, respectively, the differences in rates between the gender/sexual orientation groups were substantially attenuated. This indicates that the still high prevalence of

late presentation may be a key driver for the differences in clinical outcomes by gender/sexual orientation. It is also possible that these differences in late presentation affect the virological trends, however, pre-cART CD4 count is not usually an important factor when considering virological response to cART[462], and it is likely that this has been adjusted for to some extent by adjusting for new patient status.

In analyses of individuals currently receiving continuous cART, there was a non-linear association between calendar year and virological non-suppression. Before 2006, there were declines in the prevalence of virological non-suppression over time in all three gender/sexual orientation groups. However, since approximately 2006 there was no evidence of an improvement in virological non-suppression in any gender/sexual orientation groups. It is important to consider whether this means that levels of non-suppression seen in 2006-14 represent a "best case scenario" beyond which improvements are not possible. However, although differences were quite small in absolute terms, the higher prevalence of virological non-suppression for MSW and women even in the post-2006 period would suggest that improvements in these two groups should be possible to achieve the levels seen in MSM. Potential reasons for virological non-suppression in the era of highly effective cART should be considered. Non-adherence to ART is the most likely reason for virological non-suppression on treatment. Although many individuals maintain high levels of adherence to treatment and achieve sustained virological suppression, cART is a life-long treatment, and short periods of low- or non-adherence and associated viral breakthroughs are likely to occur for some individuals[570]. Even in recent years, a substantial proportion of individuals were diagnosed with HIV with a low CD4 count[210;543] (thus starting cART at a more advanced HIV stage[96]), which may complicate treatment, compromise virological response and result in higher levels of virological non-suppression than may be optimally achieved.

Among individuals who ever started cART, from 2006 onward there was some evidence of a decreasing prevalence of virological non-suppression among MSM and women, although not among MSW. The fact that there were declines under this analysis strategy, but not using the first analysis strategy over the same period, indicates that these improvements may be a result of fewer treatment disruptions/discontinuations over time[571-573], which were excluded in the "currently receiving cART" analysis. There was some evidence that the difference in prevalence of virological non-suppression between MSW and both MSM and women increased between 2006 and 2014, thus perhaps treatment disruptions had not declined as much among MSW. There may also be some barriers to virological suppression that affect MSW to a greater extent than MSM or women. These may include barriers to

engagement with medical care, such as experiences of stigma[574;575], factors that could impact on adherence to ART, and factors that may potentially impact on virological outcomes independently of adherence, such as late diagnosis[210;576].

In addition to differences in virological outcome between MSM and the heterosexual groups, women had a 26% lower adjusted PR of VL >50 copies/mL than MSW among individuals currently receiving cART. However, this was only found in the main analysis in this particular sub-population. Due to the inconsistency of this result under different analysis strategies, it should be interpreted with caution.

Methodologically, this chapter draws attention to the impact of choice of denominator on the estimated prevalence of virological non-suppression. In the “currently receiving continuous cART” analysis, individuals who had interrupted treatment at the time of their VL measurement or at any time during the previous six months were excluded. Thus, this provides a “best case scenario”. On the other hand, the analysis of individuals who ever started cART may be overly pessimistic, since individuals who completely discontinue cART are included in the denominator. The prevalence of women initiating cART in pregnancy was not accounted for in this chapter. Therefore, although it is not recommended and in recent years has become less frequent, discontinuations of treatment after pregnancy may account for some of the greater prevalence of virological non-suppression among women who have ever been on cART[577;578]. There are some circumstances, even since the results of the START study in 2006[162], in which an individual may need to temporarily stop treatment. Reasons may include serious side effects or drug toxicities, development of other illnesses where concurrent treatment is not possible (drug interactions), and to participate in a clinical trial. Therefore, there are advantages and disadvantages to both denominators. In the current era, non-adherence to treatment and short-term interruptions are the main predictors of poorer virological response[199], and as such, they are likely mediators for associations between gender/sexual orientation and VL non-suppression among cART-treated individuals. Thus the “ever on cART” analysis, which allows for the variability in virological response according to differences in treatment disruptions, may be the most relevant analysis in this context. However, completely discontinuing treatment is different to incomplete adherence with respect to resistance development[172], thus with respect to separating these adherence patterns, the analysis of individuals currently receiving cART offers useful information.

5.5.3 **Strengths and limitations**

One limitation of a single-centre study is external validity. The setting of the RFHCS is an urban HIV treatment centre located within a University hospital with a large patient

population and highly experienced HIV clinicians. However, the results from this study of a single clinic may still be generalisable within the UK as the study is broadly representative with respect to demographics (discussed further in Section 10.2) and the use of UK guidelines may mean that care is relatively standardised across centres. It could be argued that any disparities in virological suppression according to gender/sexual orientation may be greater in treatment centres that are newer, smaller, or have less experienced medical teams. Only individuals who had sexual transmission as the mode of HIV acquisition recorded were included in the present analysis, thus the results are not necessarily generalisable to other settings which include a large proportion of individuals who acquired HIV through non-sexual routes, such as IDU. Studies in a single clinic also have their advantages. The study population is likely to be less heterogeneous in terms of HIV care received, treatment prescribed, assays used to measure VL, etc., so the chance of confounding is reduced. An advantage of using data from the RFHCS in particular is the potential for long-term follow-up of individuals in a routine clinic setting, since the database has data on HIV-positive individuals attending for care over the past 24 years. The 100% notes review conducted annually (described in Section 4.2.5) also means that the data should be have a high degree of accuracy, particularly in terms of data collected on ART disruptions. Additionally, the RFHCS has sufficient numbers of women included to allow for assessment of gender-based (or in this case gender/sexual orientation-based) differences, unlike a number of HIV clinical trials[579].

Only those with a recorded VL (and hence were under care) were included in the analysis for each year. Thus, neither of the analysis strategies used could account for LTFU, and these results may be optimistic estimates of the improvement of virological non-suppression over time. However, my investigations suggest that LTFU is unlikely to have biased the associations between gender/sexual orientation and virological non-suppression, or trends over time, since there were similar proportions of LTFU among MSM, MSW and women and over calendar year. Although it is likely that a large proportion of the individuals recorded as LTFU may have transferred clinic and are thus not truly LTFU, it is unfortunately not easy to differentiate between this and true disengagement from care in a single-centre study. Thus, the definition of LTFU used only provides a simple measure; however, if all individuals classified as LTFU at the Royal Free Hospital were assumed to have an unsuppressed VL, the prevalence of virological non-suppression among individuals on cART would be increased by 2-8% in each year. Engagement and retention in care is very important for an individual's probability of achieving virological suppression[580-582].

It would have been beneficial to exclude pregnant women in a sensitivity analysis to see whether this could explain some of the gender/sexual orientation differences, but unfortunately these data are not routinely collected on the RFHCS. Among HIV-positive women conceiving on cART, the proportion with virological failure declined substantially from 34% in 2000–2001 to 3% in 2010–2011 in a study in Western Europe[382]. It is therefore more likely that the inclusion of pregnant women in the present analysis had a greater impact on the level of virological non-suppression in the earlier years of this analysis. In a previous study in the same setting as the analyses in this chapter, 10% of women had initiated ART in pregnancy[362]. When these women were excluded, the risk of virological rebound among women compared to MSM was lower. This indicated that starting ART in pregnancy was explaining part of the differences between these groups, however, there remained a large relative difference between these groups. It is likely that this would have been similarly the case for the analyses in this chapter.

One limitation of the statistical analyses in this chapter was that, since GEEs were used which treat longitudinal data as a series of cross-sectional time points, it was only possible to consider the population average response as opposed to subject-specific response. These models are not concerned with within-person changes. Therefore, these results should not be interpreted as "being a man who has sex with men is associated with a lower prevalence of virological non-suppression compared to being a man who has sex with women" but instead that "the prevalence of virological non-suppression is lower amongst men who have sex with men compared to men who have sex with women." This is otherwise known as the ecological fallacy. In this way, the data provide an overview of the virological status of the HIV-positive population over time, rather than providing estimates of likely virological response that one may see at an individual level.

It would have been preferable to have age standardised the death rates, since there were age differences between the gender/sexual orientation groups. However, the small numbers in the study population who died between 2000 and 2014 made this difficult (Table 5.2). Additionally, because of the aging HIV population, age categorisations that had a sufficient number of events in each group in earlier years, had insufficient numbers in the younger age categories in later years. The crude rates presented should be interpreted with caution.

5.6 **Conclusions**

This chapter provides a description of a clinic population of PLWH accessing care in the UK setting, with particular emphasis on differences by gender/ sexual orientation. Among PLWH under care between 2000 and 2014, for all gender/sexual orientation groups there have similarly been increases in cART use and improvements in immunological, virological, and clinical outcomes over time. However, MSM consistently have higher CD4 counts and higher proportion with virological suppression compared to MSW and women. Among cART-treated individuals, it is disappointing to find that MSW and women still have a higher prevalence of virological non-suppression than MSM, even in recent years, and no evidence that gender/sexual orientation disparities are narrowing over time. Further investigation is required to understand why gender/sexual orientation disparities persist and to develop interventions that may help a greater proportion of MSW and women to achieve sustained virological suppression.

Chapter 6 Initial virological responses to cART over calendar year of cART initiation – are differences by gender/sexual orientation narrowing?

6.1 Objectives

- To examine trends over calendar time in risk of virological non-suppression 12 and 24 months after starting first-line cART in the RFHCS and whether there were different for MSM, MSW, and women.
- To assess whether any differences between the gender/sexual orientation groups in risk of virological non-suppression after starting cART were narrowing or increasing in more recent years of cART initiation.
- To evaluate the extent to which a prescription-based measure of adherence and treatment disruptions accounted for differences in virological cART response.

6.2 Introduction

Previous studies in both the US and Europe have shown that the risk of an unsuppressed VL between six and 12 months after HIV treatment initiation is falling in more recent calendar years[360;457;544;583;584]. Greater antiretroviral drug (ARV) options, simpler and less toxic treatments, treatment initiation at a higher CD4 count, improvements in management and support for people starting treatment, and increasing understanding of the importance of treatment adherence are all likely to have led to improvements in initial virological response. However, this does not necessarily mean that these improvements have been experienced equally among all demographic groups affected by HIV.

As discussed in Section 2.4, a number of studies in the US and Europe found women and MSW had a poorer initial virological response to cART than MSM[357;360-362], while one recent study in EuroCoord did not find such differences[366]. In an observational study of individuals starting ART between 1996 and 2002 in European and Canadian cohorts[457], although there was evidence of greater reductions in percent with virological non-suppression over calendar time among MSM compared to MSW and women, these trends may not necessarily have continued in more recent years. Similarly, a previous study of the Royal Free HIV cohort between 2006 and 2012 found that confirmed VL >200 copies/mL at least six months after initiating cART was more common among women and MSW compared to MSM[362]. In the same study, when

individuals were not censored at complete ART discontinuation, women were identified as also being more likely to have poorer initial virological response compared to MSW. However, this study did not consider trends in ART response between these gender/sexual orientation groups over calendar time.

ART adherence is a key factor in achieving virological suppression[162-169;585], and therefore unequal improvements in adherence between the gender/sexual orientation groups may explain disparities in trends over calendar year of ART initiation in VL outcomes. Poorer adherence to treatment[126;166;376;586-591] and a greater prevalence of ART disruptions[126;189;362] among women than among men have been reported by several studies in high-income countries. Although the previous analysis of the Royal Free HIV Cohort Study (RFHCS)[362], examined gender/sexual orientation differences in ART disruptions, measures of ART adherence were not used.

6.3 **Methods**

6.3.1 **Study population**

The analyses in this chapter included individuals in the RFHCS who had a recorded sexual mode for HIV acquisition, started cART (≥ three ARVs not including RTV boosting) between January 2000 and March 2014 (baseline), aged at least 18 years, and were previously ART-naïve. The cut-off of January 2000 was chosen for the same reasons as those in Chapter 5 (Section 5.3.1). March 2014 was chosen so all participants had the potential for 18 months' follow-up before the date of administrative censoring (September 2015).

6.3.2 **Outcomes of interest**

6.3.2.1 ***Initial virological response to cART***

The primary outcome was virological non-suppression, defined as a single VL >50 copies/mL. This was examined at two time points: (i) at 12 months after starting cART, using the first VL measurement between 12 and 18 months after baseline; (ii) at 24 months, using the first VL measurement between 24 and 30 months. The reasons for defining virological non-suppression using this cut-off were discussed in Chapter 5 (Section 5.3.2) where this was also an outcome. The rationale for basing the outcome on a single binary measure, rather than using a 'time to event' approach, was that the latter approach may be more sensitive to differences in frequency of VL monitoring over calendar time, or between gender/sexual orientation groups.

6.3.2.2 *Treatment disruptions*

HIV treatment disruptions within 12 months of cART initiation were also considered. Two binary outcomes were defined: cART interruption (yes/no); and cART disruption (yes/no). Individuals were classified as having had a cART interruption if they had completely discontinued cART for at least seven consecutive days (including those who stopped and restarted or who were on "treatment holidays"), and all other individuals were classified as no interruption. Individuals were classified as having had a cART disruption if they had made any changes to their cART regimen (including discontinuing one or more ARVs), since switching regimens can be a maker for current regimen failure or adherence difficulties. Individuals who had made a change to their ART regimen other than completely discontinuing ART for at least seven days were classified as other cART disruptions. Individuals were classified as having had no cART disruptions if they were on the same regimen for the entire 12-month period.

6.3.2.3 *Treatment non-adherence*

An adherence measure was derived from the RFHCS prescription coverage data (described in Section 4.2.4.3). It was defined by calculating the number of days in a set period that an individual was covered by a prescription for at least three ARVs and then dividing this by the total number of days in the period, and multiplying by 100. This produces an adherence percentage. The period considered was three to 12 months following cART initiation, since 100% adherence for the first three months was required as an inclusion criterion in order to ensure individuals had actually initiated cART and were collecting prescriptions (see Section 6.3.3 below). Over this period, I considered two definitions of non-adherence as outcomes: (i) <95% adherence, and (ii) <80% adherence. These binary variables were chosen as there was evidence of their clinical relevance to the percentage of adherence required for virological suppression. In 2000, Paterson et al. found that un-boosted protease inhibitors required >95% adherence for optimised virological response[199]. However, recent studies of modern ARVs suggest that 80% adherence is sufficient[325;384;474;475;592;593]. Although adherence to one drug has been previously shown to be strongly associated with adherence to other drugs in the regimen[594], it is possible that adherence may differ between drugs. Thus, adherence to a triple ARV regimen (cART) was considered as opposed to one ARV. Pharmacy adherence measures have been regarded as reasonable methods to assess HIV treatment adherence when other resources are unavailable[595].

6.3.3 **Inclusion criteria**

Individuals were required to have: ≥1 VL and CD4 count measurement before cART initiation (closest within three months before starting cART and seven days after), so

that we could conduct analyses adjusted for baseline VL and CD4 count; and at least one follow-up measurement after the date of cART initiation in order to measure the virological outcome.

In addition, analyses in which measures of ART non-adherence were included were restricted to people who had: (i) an ARV prescription within a week of the date that they initiated cART, and (ii) at least one further ARV prescription between one and three months after cART initiation. These criteria were chosen to ensure that individuals had started cART at the Royal Free Hospital and were collecting prescriptions from the hospital pharmacy rather than elsewhere.

Individuals were not excluded on the basis of whether they were taking the recommended ART regimen or not as I wanted to gain a picture of the complete HIV positive population at that time. Although from 2003 unboosted PIs were no longer recommended by BHIVA, individuals on such regimens were included in the analysis to reflect changes over time. This includes both the time before they were no longer recommended and the transition period afterwards to switch individuals onto recommended regimens.

6.3.4 **Covariates of interest**

The main covariates of interest were gender/sexual orientation (defined in Section 4.4.1 and in the same way as Chapter 5) and calendar year of cART initiation. Year of cART initiation was considered as a categorical variable for descriptive purposes in initial analyses. It was categorised into seven groups (six groups for 24-month outcomes) so that there were sufficient numbers in each group in order to permit meaningful patterns to emerge: 2000-01, 2002-03, 2004-05, 2006-07, 2008-09, 2010-11, and 2012-14 (the final two groups were merged for the 24-month outcomes). It was also used as a continuous variable in multivariable statistical models when assessment of linear trend over calendar time of cART initiation was the primary interest.

The other baseline covariates considered were:

- Age (continuous),
- VL (<10,000; 10,000-99,999; ≥100,000 copies/mL),
- CD4 count (≥350; 200-349; <200 cells/μL),
- Initial cART regimen type (NNRTI-based; PI-based; other).

Age was considered as that at the date of ART initiation. For baseline VL, baseline CD4 count and initial cART regimen, the values taken were those closest to the date of ART initiation as long as this date was no later than a week after ART initiation. These variables were chosen based on previous evidence in the literature that they are predictors of virological response to cART[92;131;596-599]. In particular, in the previous RFHCS analysis described in Section 6.2, with the exception of baseline CD4 count, these covariates were found to be associated with virological response[457]. Baseline CD4 count was included in the model for the analyses in this chapter as it may be a potential confounder, since up until 2015 the timing of cART initiation was recommended to be based upon CD4 count (see Section 1.3.2.1)[133;138;139].

6.3.5 **Statistical analysis**

For the analyses with virological non-suppression as the outcome, three analysis strategies were used:

- Strategy A: missing=failure
  All individuals who had started cART were included, but individuals with no VL measurements between 12-18 months (or 24-30 months for the 24-month time-point) were considered to have virological non-suppression.
- Strategy B: missing=excluded
  Only those with at least one recorded VL between 12-18 months (or 24-30 months for the 24-month time-point) were included.
- Strategy C: on cART
  Only those who were on cART at the time of the recorded VL were included.

Strategy B was considered the primary analysis. For the analyses with treatment disruptions and treatment non-adherence as outcomes, only strategy B was used.

The association between gender/sexual orientation and each outcome at 12 and 24 months (virological non-response; treatment interruption, treatment disruption and non-adherence) were summarised using risk ratios (RRs). These were calculated using modified Poisson regression (detailed in Section 4.5.4.1). Univariable models were first used, and then multivariable models that additionally included: calendar year of cART initiation; age at baseline; baseline VL; baseline CD4 count; cART regimen at baseline. Evidence for differences in the trend over year of cART initiation by gender/sexual orientation were then assessed by additionally including interaction terms in the model.

Among individuals with cART disruptions, the clinician-reported reasons for stopping any ARV within 12 months of cART initiation were summarised by gender/sexual orientation group.

In addition to being considered as outcomes, cART non-adherence and cART disruptions were also considered as mediators of the association between gender/sexual orientation and virological non-suppression (i.e. considered as covariates in the analysis with a virological non-suppression outcome). If the effects of gender/sexual orientation on virological response act through cART non-adherence or disruptions, then the inclusion of either factor in multivariable models would be expected to attenuate any observed associations between gender/sexual orientation and virological non-suppression to some extent. It is important to appreciate that the extent to which any factor has the potential to "explain" variation across gender/sexual orientation groups in non-adherence/virological outcomes, is dependent on the validity of the factor in capturing what it is intended to measure, and the amount of measurement error. Therefore, just as an association between an exposure and an outcome may be over or underestimated in the presence of measurement error, the amount by which a factor "explains" the association between an exposure and an outcome may also be over or underestimated in this situation[600;601]. By using this method, one also assumes that the underlying mechanism of correlation (i.e. how one factor affects the other) between the covariates is correctly specified. When considered as a mediator, cART adherence was defined as continuous percentage coverage due to previous evidence of a dose-response relationship between prescription based adherence and virological suppression[199;325]. cART disruption was considered as a three-category variable (interrupted - completely discontinued cART for at least seven consecutive days; all other cART disruptions; no disruptions) to assess how each distinct behaviour was related to treatment response.

6.3.6 **Sensitivity analyses**

For the 12-month virological non-suppression analyses, three sensitivity analyses were performed. In the first, virological non-suppression was redefined as a single VL measurement >200 copies/mL (rationale explained in Section 5.3.6). In the second, individuals without a VL or CD4 count measurement in the three months before cART initiation. This analysis was conducted since 739 individuals (27% of otherwise eligible individuals) were excluded due to these criteria, which could have led to selection bias. In the third sensitivity analysis, the outcome of virological non-suppression was defined as individuals with a VL >50 copies/mL at 12 months as in the main analysis, however using the closest VL to 12 months but between six and 18 months after cART

initiation rather than between 12 and 18 months. In the past, individuals with HIV receiving ART were recommended to be seen by a physician, and have their VL measured, every three to four months. However, once on successful ART, this may be extended to six-monthly[552;602;603]. Thus, individuals doing well on treatment may be less likely to have visited in the 12-18 month window and so a wider window of 6-18 months may be more appropriate.

6.3.7 **Missing data**

By the inclusion criteria, individuals with missing gender/sexual orientation, age, baseline VL, baseline CD4 count, cART regimen type were excluded. Likewise, for the analyses that included the measure of cART non-adherence, the population was restricted to those with prescription data. Therefore, the individuals included in this analysis had no missing data for any of the covariates of interest. As described above, in a sensitivity analysis, individuals with missing baseline VL and CD4 count were included, except for the models which include baseline VL and CD4 count as covariates. This provided some limited information on the potential impact of missing data on study results. Furthermore, analysis strategy A categorised individuals with missing outcome data as having poorer outcomes, whereas analysis strategies B and C exclude individuals with missing data, providing some information on the impact on results of missing virological outcome data.

6.4 **Results**

6.4.1 **Virological non-suppression at 12 months**

6.4.1.1 ***Participant characteristics***

The RFHCS database included 6423 individuals in September 2015. Of these, 2937 started cART between January 2000 and March 2014, 2757 reported likely acquiring HIV sexually, of whom 2753 were over 18 years old at the time of starting cART. Further exclusions were as follows: 782 had no baseline VL recorded, or no baseline CD4 count, or no VL measurements after cART initiation. This resulted in 1971 individuals (67% of individuals who started cART between 2000 and 2014) included in the analyses. Note that 40 (1%) individuals died before they were able to have a VL measurement 12-18 months after cART initiation. These individuals were included in analysis strategy A as virologically non-suppressed but were excluded from analyses under strategies B and C.

For strategy A all 1971 individuals were included in the analyses: 1049 (53%) MSM; 372 (19%) MSW; 550 (28%) women. For strategy B, a further 356 (18% of those included in strategy A) individuals were excluded because they had no VL measurement 12-18 months after baseline, resulting in 1615 individuals: 877 (54%) MSM; 292 (18%) MSW; 446 (28%) women. Finally, for strategy C, a further 93 individuals were excluded because they were not on cART at the time of the VL measurement. This left 1522 individuals included in analysis C: 837 (55%) MSM; 283 (19%) MSW; 402 (26%) women.

The characteristics of the study population by gender/sexual orientation for each analysis strategy is displayed in Table 6.1. MSW and women were more likely than MSM to be of black African ethnicity. MSW had an older median age than MSM, and particularly compared to women. The initial cART regimens started were similar between the three gender/sexual orientation groups. A small percentage, <6% for all groups, initiated a cART regimen other than ≥2 NRTI's with either a PI or NNRTI as the third ARV (for strategy A: 2.25% raltegravir; 0.05% dolutegravir; 0.15% maraviroc; 3.40% ≥3 NRTI; 1.07% on a PI and NNRTI). MSM had the highest median baseline CD4 count, followed by women and then MSW. However, CD4 count at starting ART was low across all groups, and the median CD4 for women and MSW was below 200 cells/μL. Correspondingly, women and MSW were more likely to have had an ADE or CD4 count <200 cells/μL before cART initiation compared to MSM, and a marginally higher median VL at baseline than MSM.

Table 6.1: Characteristics at the time of cART initiation of individuals included in the analysis of virological response to cART at 12 months after initiation

Factors		Strategy A: missing=failure (N=1971)						Strategy B: missing=excluded (N=1615)						Strategy C: on cART (N=1522)					
		MSM		MSW		Women		MSM		MSW		Women		MSM		MSW		Women	
		N	%					N	%					N	%				
Overall		1063	53%	372	19%	554	28%	877	54%	292	18%	446	28%	790	55%	266	19%	374	26%
Calendar year of cART initiation	2000-01	122	12%	43	12%	71	13%	99	11%	29	10%	54	12%	94	11%	29	10%	46	11%
	2002-03	156	15%	75	20%	84	15%	133	15%	60	21%	70	16%	124	15%	58	10%	63	16%
	2004-05	151	14%	52	14%	82	15%	139	16%	45	15%	73	16%	131	16%	43	15%	62	15%
	2006-07	156	15%	65	17%	106	19%	128	15%	49	17%	81	18%	120	14%	48	17%	69	17%
	2008-09	176	17%	57	15%	92	17%	156	18%	47	16%	73	16%	152	18%	46	16%	71	18%
	2010-11	150	14%	39	10%	63	11%	132	15%	33	11%	54	12%	128	15%	31	11%	51	13%
	2012-14	138	13%	39	10%	52	9%	90	10%	29	10%	41	9%	88	11%	28	10%	40	10%
Ethnicity	White	856	82%	90	24%	80	15%	715	82%	78	25%	66	15%	682	81%	77	27%	62	15%
	Black African	18	2%	194	52%	353	64%	13	1%	147	51%	289	65%	13	2%	141	50%	255	63%
	Other	96	9%	69	19%	85	15%	81	9%	53	19%	64	14%	77	9%	51	18%	61	15%
	Missing	79	8%	19	5%	32	6%	68	8%	14	5%	27	6%	65	8%	14	5%	24	6%
cART regimen base	NNRTI	536	51%	203	54%	262	48%	433	49%	154	53%	201	45%	418	50%	151	53%	188	47%
	PI	472	45%	155	42%	260	47%	410	47%	127	43%	220	49%	386	46%	123	43%	191	48%
	Other	41	4%	124	4%	28	5%	34	4%	11	4%	25	6%	33	4%	9	3%	23	6%
Previous ADE		124	12%	110	30%	133	24%	108	12%	85	29%	109	24%	105	13%	82	29%	104	26%
Previously CD4 ≤200		389	37%	229	62%	325	59%	325	37%	179	61%	254	57%	318	38%	174	61%	248	62%
		Median (IQR)						Median (IQR)						Median (IQR)					
Age (years)		38 (33, 44)		40 (34, 47)		36 (30, 43)		38 (33, 44)		40 (34, 47)		36 (30, 42)		38 (33, 45)		40 (34, 47)		37 (31, 43)	
Baseline CD4 count (cells/μL)		274 (169, 400)		163 (52, 275)		194 (79, 300)		273 (170, 407)		170 (53, 284)		202 (80, 303)		270 (167, 392)		168 (53, 286)		188 (70, 279)	
Baseline VL (log copies/mL)		5.0 (4.5, 5.5)		4.9 (4.4, 5.5)		4.8 (4.1, 5.4)		5.0 (4.5, 5.5)		4.9 (4.4, 5.5)		4.8 (4.1, 5.4)		5.0 (4.5, 5.5)		4.9 (4.3, 5.5)		4.9 (4.2, 5.4)	

Results in **bold** had a P-value of <0.05 when assessed using Chi-squared tests for categorical variables or Wilcoxon-Mann-Whitney tests for continuous variables; NNRTI= Non-Nucleoside Reverse Transcriptase Inhibitors; PI= Protease Inhibitors; IQR= interquartile range; ADE= AIDS defining event.

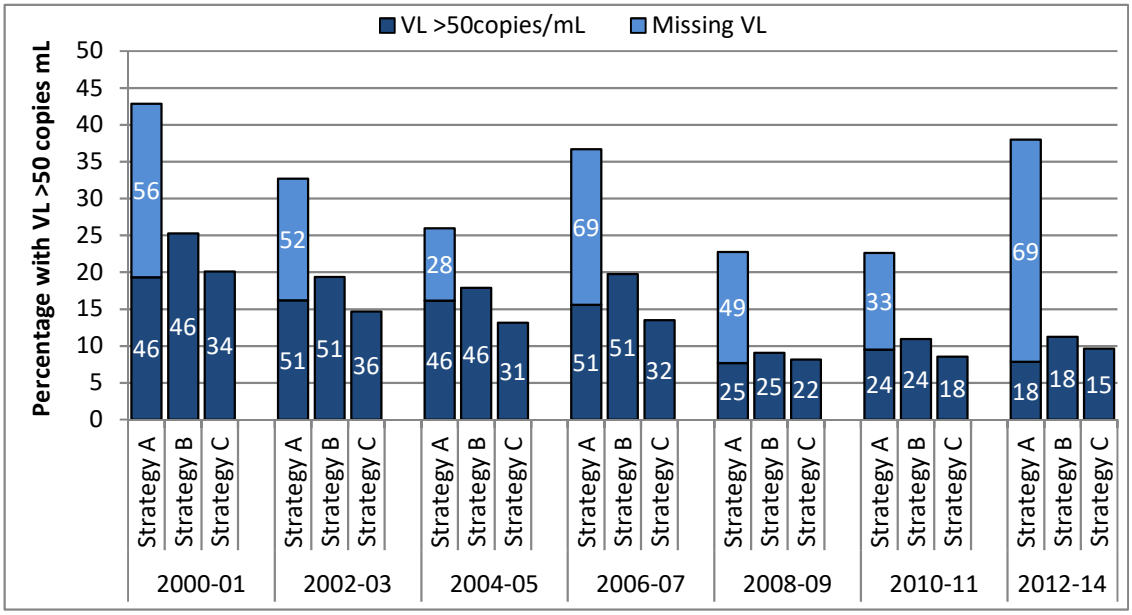
6.4.1.2 *Prevalence of virological non-suppression 12 months after cART initiation*

By calendar year of cART initiation

Using strategy A, 617/1971 (31%) individuals were defined as virologically non-suppressed at 12 months: 356 (58%) with missing VL; and 261 (42%) with VL >50 copies/mL (100 individuals with 50-200 copies/mL; 43 with 200-1000 copies/mL; 46 with 1000-10000 copies/mL; 72 with >10,000 copies/mL). Using strategy B, for which individuals with missing VL were excluded, 261/1615 (16%) individuals had virological non-suppression at 12 months. Finally using strategy C, for which individuals with a missing VL or who were not on cART at the time of the VL measurement were excluded, 188/1522 (12%) individuals had virological non-suppression at 12 months.

The percentage of individuals with virological non-suppression 12 months after cART initiation by calendar year for each strategy are shown in . Using strategy A, virological non-suppression was neither increasing nor decreasing with more recent year of cART initiation. However, those categorised as virologically non-suppressed were dominated by individuals lost to follow-up (LTFU) in more recent years. There was a greater prevalence of missing VL measurement 12-18 months after cART initiation over calendar year of cART initiation ($p<0.0001$) and a decreasing prevalence of VL >50 copies/mL ($p<0.0001$) which offset one another. Under analysis strategies B ($p<0.0001$ Cochran-Armitage test for trend) and C ($p=0.0038$) the prevalence of virological non-suppression was decreasing over calendar year of cART initiation. Under strategy B, 25% of individuals had VL >50 copies/mL at 12 months in 2000-01, which fell to 11% in 2012-14.

Figure 6.1: Percentage with virological non-suppression 12-18 months after cART initiation by calendar year of cART initiation according to analysis strategy

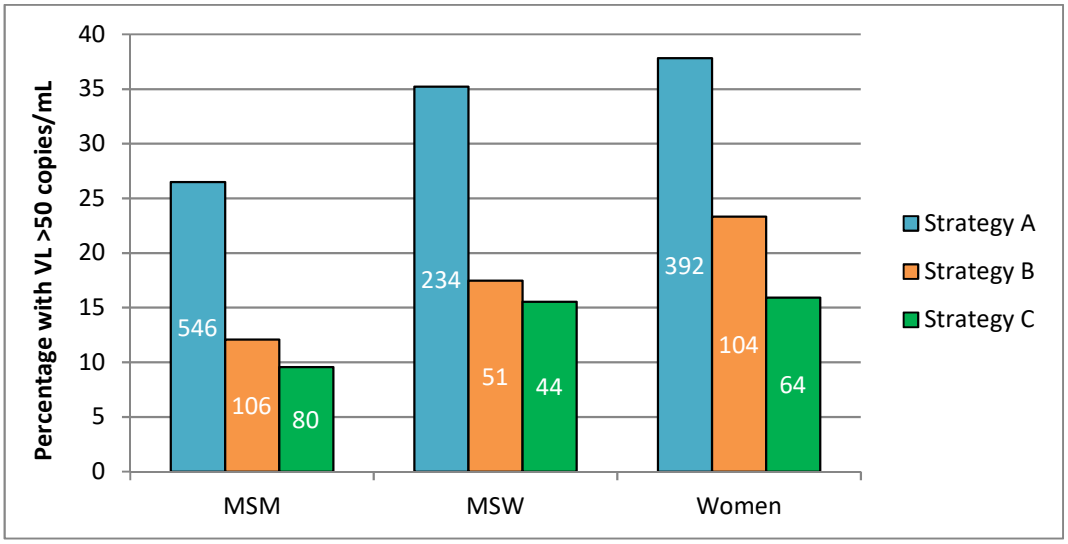


Numbers on each bar represent the number of individuals in that category. Strategies A, B, C defined in Section 6.3.5.

By gender/sexual orientation

A substantially greater percentage of MSW and women had virological non-suppression compared to MSM under all three analysis strategies (for strategies A, B, and C $p<0.0001$; $p<0.0001$; $p=0.0012$ by chi squared test) as shown in Figure 6.2. However, this was averaged over all calendar years of cART initiation, which was shown to be associated with decreasing prevalence of virological non-suppression.

Figure 6.2: Percentage with virological non-suppression 12-18 months after cART initiation by gender/sexual orientation according to analysis strategy



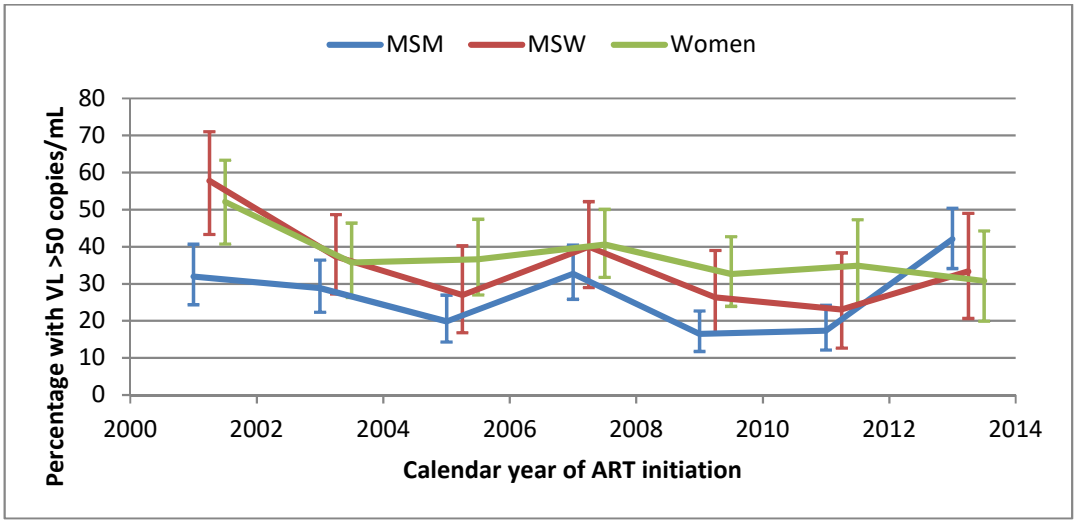
Numbers on each bar represent the number of individuals with VL >50 copies/mL in that category; strategies A, B, C defined in Section 6.3.5.

6.4.1.3 *Association between gender/sexual orientation, calendar year of cART initiation and virological non-suppression 12-18 months after cART initiation*

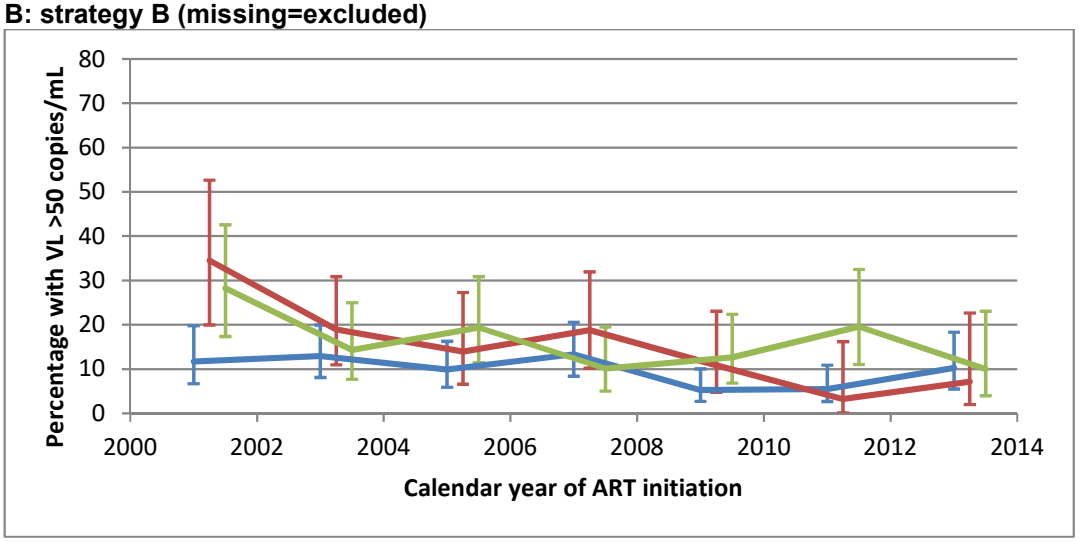
Generally, the risk of virological non-suppression at 12 months was lower in more recent calendar year of starting cART for all gender/sexual orientation groups and all analysis strategies (Figure 6.3A, B and C). A greater percentage of MSW and women had virological non-suppression at 12 months compared to MSM at most calendar years of cART initiation. Considering strategy B for example, of 182 individuals starting cART in 2000-01, 16.2% of MSM, 34.5% of MSW and 37.0% of women had virological non-suppression 12 months after cART initiation. For the 160 individuals starting cART in 2012-14, these values were 11.1%, 10.3% and 12.2% respectively.

Figure 6.3: Percentage with virological non-suppression 12-18 months after cART initiation over calendar year of cART initiation stratified by gender/sexual orientation

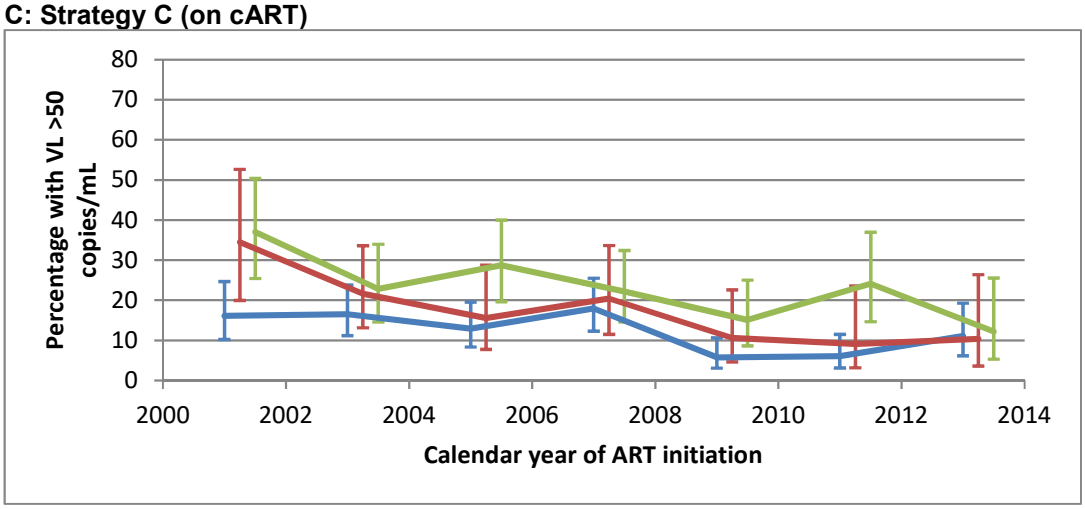
A: Strategy A (missing=failure)



B: strategy B (missing=excluded)



C: Strategy C (on cART)



Denominators are provided in Table 6.1; the bars on graph represent confidence intervals.

The association between gender/sexual orientation and virological non-suppression can also be seen in terms of RRs in Table 6.2, Table 6.3 and Table 6.4 for analysis strategies A, B and C respectively. Across all three analysis strategies, women and MSW had a greater risk of virological non-suppression at 12 months compared to MSM. In analyses adjusted for calendar year of cART initiation, age, baseline VL, baseline CD4 count, and initial cART regimen, MSW had 1.4-1.6 times higher risk of virological non-suppression at 12 months after cART initiation than MSM across the three analysis strategies. Similarly, women had 1.4-1.9 times higher adjusted risk of virological non-suppression at 12 months compared to MSM. MSW and women generally had a similar risk of virological non-suppression. 'MSW vs MSM' differences were similar in the adjusted compared to unadjusted analysis, whereas 'women vs MSM' differences tended to be somewhat attenuated. There was an adjusted risk reduction of 2-8% per additional calendar year of cART initiation across the three analysis strategies. This shows that initial virological response had improved over time since 2000, even after accounting for changes in characteristics of people starting cART and, broadly, for type of starting regimen.

Of the other factors included in the multivariable model, higher adjusted risk of virological non-suppression was associated with younger age and baseline VL <10000 copies/mL (Table 6.2 Table 6.3 and Table 6.4). Baseline CD4 count <350 cells/μL was associated with higher adjusted risk of virological non-suppression under analysis strategy C, but not under the other analysis strategies. Likewise, PI- or other-based initial cART regimens were associated with a higher adjusted risk of virological non-suppression compared to NNRTI-based regimens under strategies B and C, but not A.

Table 6.2: Associations of gender/sexual orientation, calendar year of cART initiation and other baseline factors with virological non-suppression 12-18 months after cART initiation – Strategy A (missing=failure)

Factor [a]	Unadjusted			Adjusted		
	RR	95% CI	P-value [b]	aRR [c]	95% CI	P-value
Gender/ sexual orientation						
MSW vs. MSM	1.33	1.12, 1.58	<.0001	1.35	1.13, 1.60	0.0001
Women vs. MSM	1.43	1.23, 1.65		1.35	1.16, 1.58	
Women vs. MSW	1.07	0.90, 1.28		1.01	0.84, 1.20	
Calendar year of cART initiation						
Per year	0.98	0.96, 0.99	0.010	0.98	0.96, 1.00	0.053
Age						
Per 10 years	0.85	0.79, 0.92	<.0001	0.86	0.80, 0.93	0.0001
Baseline VL (copies/ mL)						
<10000	1		0.0007	1		0.029
10000-99999	0.73	0.61, 0.88		0.78	0.64, 0.93	
≥100000	0.82	0.70, 0.98		0.87	0.72, 1.05	
Baseline CD4 count (cells/μL)						
≥350	1		0.55	1		0.91
200-350	1.02	0.86, 1.22		0.96	0.81, 1.15	
<200	1.09	0.92, 1.29		0.97	0.81, 1.16	
Type of initial cART regimen						
NNRTI	1		0.77	1		0.73
PI	0.99	0.87, 1.13		0.98	0.86, 1.12	
Other	1.12	0.82, 1.52		1.12	0.83, 1.51	

[a] Each factor considered in separate univariable models then all factors in a single multivariable model; [b] likelihood ratio test; [c] adjusted for all factors listed in the table; denominators are provided in Table 6.1; RR= risk ratio; aRR= adjusted risk ratio; NNRTI= Non-Nucleoside Reverse Transcriptase Inhibitors; PI= Protease Inhibitors.

Table 6.3: Associations of gender/sexual orientation, calendar year of cART initiation and other baseline factors with virological non-suppression 12-18 months after cART initiation – Strategy B (missing=excluded)

Factor [a]	Unadjusted			Adjusted		
	RR	95% CI	P-value [b]	aRR [c]	95% CI	P-value [b]
Gender/ sexual orientation						
MSW vs. MSM	1.45	1.06, 1.96	<.0001	1.60	1.17, 2.20	<.0001
Women vs. MSM	1.93	1.51, 2.47		1.87	1.45, 2.43	
Women vs. MSW	1.34	0.99, 1.80		1.17	0.86, 1.58	
Calendar year of cART initiation						
Per year	0.93	0.90, 0.96	<.0001	0.92	0.89, 0.95	<.0001
Age						
Per 10 years	0.77	0.67, 0.88	<.0001	0.84	0.74, 0.96	0.0095
Baseline VL (copies/ mL)						
<10000	1		0.0024	1		0.0028
10000-99999	0.62	0.44, 0.86		0.67	0.48, 0.92	
≥100000	0.90	0.67, 1.22		1.00	0.73, 1.37	
Baseline CD4 count (cells/μL)						
≥350	1		0.96	1		0.093
200-350	0.97	0.72, 1.29		0.83	0.63, 1.11	
<200	1.00	0.76, 1.32		0.71	0.53, 0.96	
Type of initial cART regimen						
NNRTI	1		0.0009	1		0.0005
PI	1.51	1.19, 1.91		1.52	1.21, 1.91	
Other	1.80	1.13, 2.88		1.73	1.10, 2.73	

[a] Each factor considered in separate univariable models then all factors in a single multivariable model; [b] likelihood ratio test; [c] adjusted for all factors listed in the table; denominators are provided in Table 6.1; RR= risk ratio; aRR= adjusted risk ratio; NNRTI= Non-Nucleoside Reverse Transcriptase Inhibitors; PI= Protease Inhibitors.

Table 6.4: Associations of gender/sexual orientation, calendar year of cART initiation and other baseline factors with virological non-suppression 12-18 months after cART initiation – Strategy C (on cART)

Factor [a]	Unadjusted			Adjusted		
	RR	95% CI	P-value [b]	aRR [c]	95% CI	P-value [b]
Gender/ sexual orientation						
MSW vs. MSM	1.63	1.16, 2.29	0.0016	1.60	1.13, 2.26	0.011
Women vs. MSM	1.67	1.23, 2.26		1.50	1.09, 2.08	
Women vs. MSW	1.02	0.72, 1.46		0.94	0.66, 1.34	
Calendar year of cART initiation						
Per year	0.93	0.90, 0.97	0.0004	0.95	0.91, 0.99	0.014
Age						
Per 10 years	0.86	0.74, 1.01	0.061	0.90	0.76, 1.05	0.16
Baseline VL (copies/ mL)						
<10000	1		<.0001	1		0.0003
10000-99999	0.64	0.40, 1.01		0.65	0.41, 1.02	
≥100000	1.28	0.86, 1.91		1.23	0.80, 1.88	
Baseline CD4 count (cells/µL)						
≥350	1		<.0001	1		0.043
200-350	1.86	1.20, 2.89		1.66	1.07, 2.58	
<200	2.22	1.46, 3.37		1.56	0.99, 2.47	
Type of initial cART regimen						
NNRTI	1		0.019	1		0.0041
PI	1.42	1.08, 1.88		1.51	1.15, 1.98	
Other	1.84	1.06, 3.20		1.96	1.14, 3.37	

[a] Each factor considered in separate univariable models then all factors in a single multivariable model; [b] likelihood ratio test; [c] adjusted for all factors listed in the table; denominators are provided in Table 6.1; RR= risk ratio; aRR= adjusted risk ratio; NNRTI= Non-Nucleoside Reverse Transcriptase Inhibitors; PI= Protease Inhibitors.

6.4.1.4 *Interaction between gender/sexual orientation and calendar year of cART initiation*

To evaluate whether the trend of lower risk of virological non-suppression with more recent calendar year was different between the gender/sexual orientation groups, models including interaction terms were assessed. These results are displayed in Table 6.5. The adjusted RRs in this table represent the estimated slope for virological non-suppression over calendar year of cART initiation, within each gender/sexual orientation group. Considering strategy B for example, MSM had, on average, a 7% lower risk of virological non-suppression per more recent year that cART was initiated. In comparison, this was 10% and 7% lower risk per year for MSW and women, respectively. Although this trend estimate was greatest among MSW, there was no statistically significant difference between the groups (p=0.72). Thus, there was no evidence that the differences between the gender/sexual orientation groups in virological non-suppression risk were narrowing or widening. This concurred with results for analysis strategy C. However, there was evidence that the differences between the groups were narrowing under analysis strategy A: 5% and 4% reduced risk per calendar year more recently cART was initiated among MSW and women, respectively, and no reduction among MSM. The differences using this strategy likely reflected differences in LTFU in the year group 2012-2015. When the individuals initiating ART in these years were excluded there was no evidence of an interaction (p=0.53).

Table 6.5: Associations of the interaction between gender/sexual orientation and calendar year of cART initiation with virological non-suppression 12-18 months after cART initiation, according to analysis strategy

		Strategy A (missing=failure)			**Strategy B (missing=excluded)**			**Strategy C (on cART)**		
		aRR [a]	95% CI	P-value[b]	aRR [a]	95% CI	P-value[b]	aRR [a]	95% CI	P-value[b]
Relative change per calendar year of cART initiation	MSM	1.01	0.98, 1.03	0.041	0.93	0.88, 0.97	0.72	0.97	0.92, 1.03	0.19
	MSW	0.95	0.92, 0.99		0.90	0.83, 0.97		0.89	0.81, 0.97	
	Women	0.96	0.94, 0.99		0.93	0.88, 0.98		0.96	0.90, 1.03	

[a] Adjusted for age, baseline VL and CD4 count, initial cART regimen; [b] likelihood ratio test for interaction term; aRR= adjusted risk ratio.

6.4.2 **Virological non-suppression 24-30 months after cART initiation**

6.4.2.1 ***Participant characteristics***

Of the 1971 individuals in the 12 month analysis, I excluded a further 100 people that started cART between March 2013 and March 2014 to ensure that all individuals in this analysis had the potential for 30 months follow-up. This resulted in 1871 individuals (67% of all individuals who started cART between 2000 and 2013) included in the analyses of virological non-suppression at 24 months.

For analysis strategy A, all 1871 were included: 989 (53%) MSM; 356 (19%) MSW; 526 (28%) women. In strategy B, a further 461 were excluded because they had no VL measurement 24-30 months after baseline, which resulted in 1410 individuals: 775 (55%) MSM; 257 (18%) MSW; 378 (27%) women. Finally, for strategy C, a further 99 were excluded because they were not on cART at the time of the VL measurement 24-30 months after baseline, which left 1311 individuals included: 722 (55%) MSM; 247 (19%) MSW; 342 (26%) women. The characteristics of the study population by gender/sexual orientation are displayed in Table 6.6 and were similar to those in the 12-month analyses.

Table 6.6: Characteristics of individuals included in the analysis of virological non-suppression 24-30 months after cART initiation

Factors		Strategy A: missing=failure (N=1871)						Strategy B: missing=excluded (N=1410)						Strategy C: on cART (N=1311)					
		MSM		MSW		Women		MSM		MSW		Women		MSM		MSW		Women	
		N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%
Overall		989	53%	356	19%	526	28%	775	55%	257	18%	378	27%	722	55%	247	19%	342	26%
Calendar year of cART initiation	2000-01	122	12%	45	13%	71	14%	93	12%	35	14%	47	12%	84	12%	33	13%	41	12%
	2002-03	156	16%	75	21%	84	16%	134	17%	53	21%	67	18%	123	17%	52	21%	59	17%
	2004-05	151	15%	52	15%	82	16%	122	16%	34	13%	64	17%	110	15%	32	13%	55	16%
	2006-07	156	16%	65	18%	106	20%	127	16%	47	18%	77	20%	121	17%	46	19%	72	21%
	2008-09	176	18%	57	16%	92	17%	144	19%	47	18%	69	18%	135	19%	44	18%	64	19%
	2010-13	228	23%	62	17%	91	17%	155	20%	41	16%	54	14%	149	21%	40	16%	51	15%
Ethnicity	White	**809**	**82%**	**84**	**24%**	**70**	**13%**	**628**	**81%**	**65**	**25%**	**54**	**14%**	**582**	**81%**	**62**	**25%**	**51**	**15%**
	Black African	**17**	**2%**	**189**	**53%**	**342**	**65%**	**11**	**1%**	**131**	**51%**	**246**	**65%**	**10**	**1%**	**127**	**51%**	**220**	**64%**
	Other	**89**	**9%**	**64**	**18%**	**82**	**16%**	**74**	**10%**	**48**	**19%**	**59**	**16%**	**70**	**10%**	**45**	**18%**	**54**	**16%**
	Missing	**74**	**7%**	**19**	**5%**	**32**	**6%**	**62**	**8%**	**13**	**5%**	**19**	**5%**	**60**	**8%**	**13**	**5%**	**17**	**5%**
cART regimen base	NNRTI	507	51%	194	54%	247	47%	394	51%	145	56%	174	46%	379	52%	139	56%	164	48%
	PI	446	45%	150	42%	253	48%	356	46%	104	40%	185	49%	321	44%	102	41%	159	46%
	Other	36	4%	12	3%	26	5%	25	3%	8	3%	19	5%	22	3%	6	2%	19	6%
Previous ADE		**121**	**12%**	**104**	**29%**	**128**	**24%**	**97**	**13%**	**74**	**29%**	**96**	**25%**	**96**	**13%**	**70**	**28%**	**92**	**27%**
Previously CD4≤200		**380**	**38%**	**222**	**62%**	**313**	**60%**	**295**	**38%**	**157**	**61%**	**229**	**61%**	**285**	**39%**	**150**	**61%**	**221**	**65%**
		Median (IQR)						Median (IQR)						Median (IQR)					
Age	Years	**38 (33, 44)**		**40 (34, 46)**		**36 (30, 42)**		**38 (33, 44)**		**40 (34, 47)**		**36 (30, 42)**		**38 (33, 45)**		**40 (34, 47)**		**36 (31, 42)**	
Baseline CD4 count	Cells/μL	**269 (165, 388)**		**158 (52, 268)**		**194 (80, 292)**		**269 (167, 390)**		**160 (55, 268)**		**193 (75, 291)**		**261 (163, 382)**		**160 (53, 281)**		**185 (71, 266)**	
Baseline VL	Log copies/mL	**5.0 (4.5, 5.5)**		**4.9 (4.4, 5.5)**		**4.8 (4.1, 5.4)**		**5.0 (4.5, 5.5)**		**5.0 (4.4, 5.5)**		**4.8 (4.1, 5.4)**		**5.0 (4.5, 5.5)**		**4.9 (4.3, 5.5)**		**4.8 (4.2, 5.4)**	

Results in **bold** had a P-value of <0.05 when assessed using Chi-squared tests for categorical variables or Wilcoxon-Mann-Whitney tests for continuous variables; NNRTI= Non-Nucleoside Reverse Transcriptase Inhibitors; PI= Protease Inhibitors; IQR= interquartile range; ADE= AIDS defining event.

6.4.2.2 *Percentage with virological non-suppression 24-30 months after cART initiation*

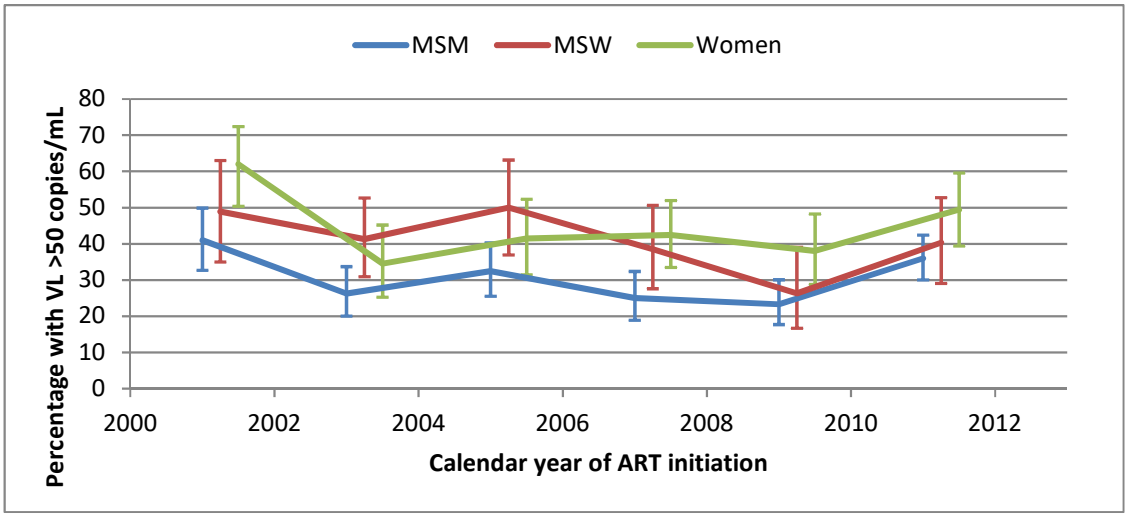
Using strategy A, 678/1871 (36%) individuals had virological non-suppression at 24 months (461 with a missing VL, 217 with VL >50 copies/mL). In comparison, 217/1410 (15%) individuals had virological non-suppression at 24 months using strategy B, and 149/1311 (11%) individuals using strategy C.

6.4.2.3 *Gender/sexual orientation, calendar year of cART initiation and virological non-suppression 24-30 months after cART initiation*

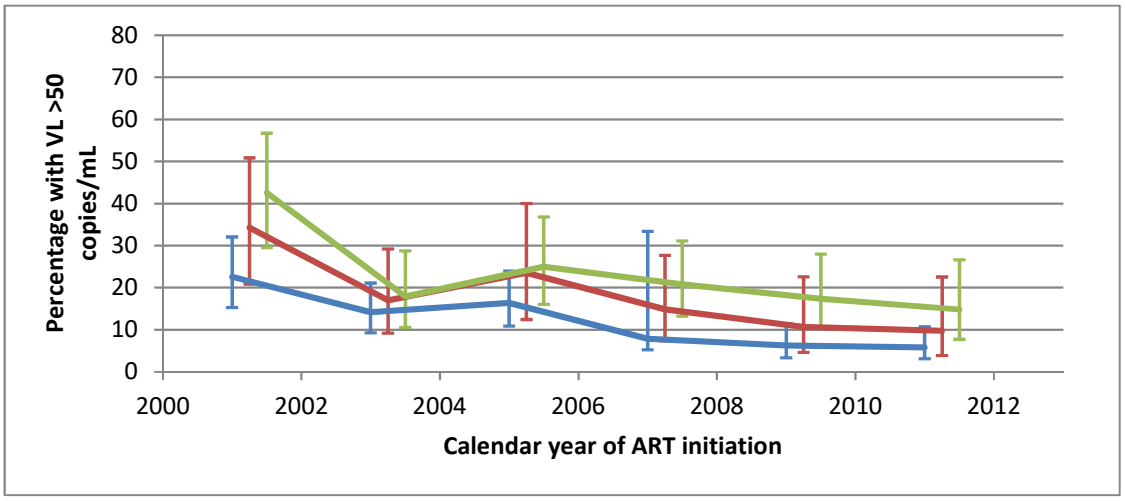
As with virological non-suppression at 12 months, the risk of virological non-suppression at 24 months after cART initiation decreased in more recent years among all three groups (Figure 6.4a, b and c). A higher percentage of women and MSW than MSM had virological non-suppression at 24 months after cART initiation across all time points and for each of the analysis strategies. The prevalence of virological non-suppression among MSW intersected with that among women at various points, showing the similarity in virological response between these two groups. Under analysis strategy B, of those starting cART in 2000-01, 23% of MSM, 34% of MSW and 43% of women had a VL >50 copies/mL at 24 months. For those starting cART in 2010-13, these values were 6%, 10% and 15% respectively.

Figure 6.4: The percentage of individuals with virological non-suppression at 24-30 months after cART initiation over calendar year of cART initiation and stratified by gender/sexual orientation using analysis strategy A (missing=failure)

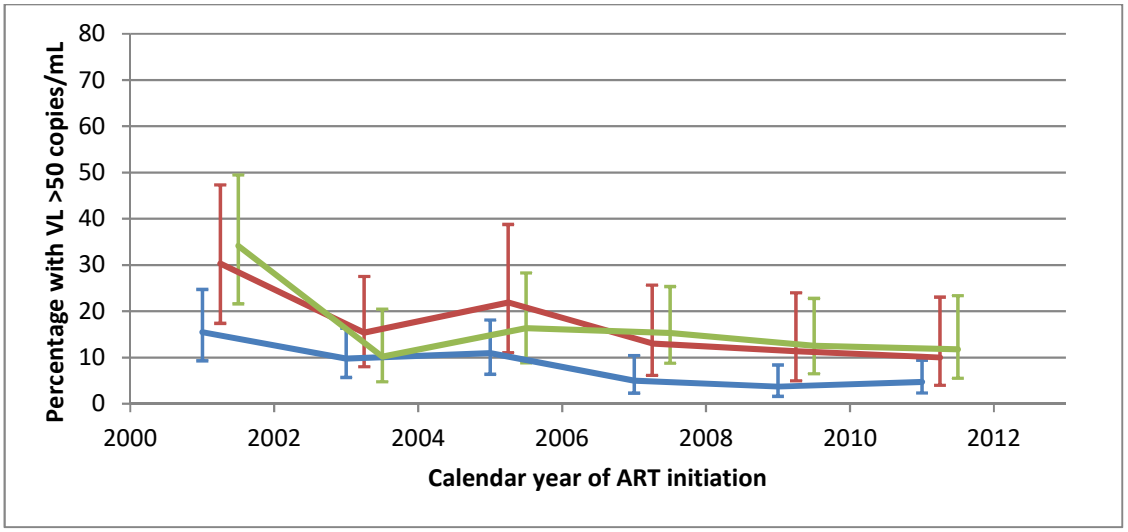
A: Strategy A (missing=failure)



B: Strategy B (missing=excluded)



C: Strategy C (on cART)



Denominators are provided in Table 6.6; the bars on graph represent confidence intervals.

Unadjusted and adjusted RRs for the association of gender/sexual orientation with virological non-suppression at 24 months after cART initiation are displayed in Table 6.7, Table 6.8 and Table 6.9. MSW and women were at a greater risk of virological non-suppression compared to MSM across all three strategies. Compared to MSM, the adjusted RRs were 1.4-2.0 for MSW and 1.4-1.9 for women. MSW and women had a similar risk of virological non-suppression. Calendar year of cART initiation was not associated with virological non-suppression at 24 months for analysis strategy A. However, for analysis strategies B and C for every year more recently that cART was initiated, individuals were, on average, at a 11% and 7% reduced adjusted risk of virological non-suppression at 24 months, respectively. For the other variables included in multivariable analyses, the associations with virological non-suppression were similar to those in the 12-month analysis.

Table 6.7: Associations of gender/sexual orientation, calendar year of cART initiation and other factors at baseline with virological non-suppression 24-30 months after cART initiation - Strategy A (missing=failure)

Factor [a]	Unadjusted			Adjusted		
	RR	95% CI	P-value [b]	aRR [c]	95% CI	P-value [b]
Gender/ sexual orientation						
MSW vs. MSM	1.32	1.13, 1.55	<.0001	1.35	1.15, 1.59	<.0001
Women vs. MSM	1.44	1.26, 1.65		1.39	1.21, 1.60	
Women vs. MSW	1.09	0.93, 1.28		1.03	0.88, 1.21	
Calendar year of cART initiation						
Per year	0.99	0.87, 1.01	0.19	0.99	0.98, 1.01	0.53
Age						
Per 10 years	0.85	0.81, 0.93	<.0001	0.88	0.82, 0.94	0.0002
Baseline VL (copies/ mL)						
<10000	1		0.15	1		0.41
10000-99999	0.73	0.70, 1.00		0.90	0.76, 1.07	
≥100000	0.82	0.76, 1.06		0.96	0.81, 1.15	
Baseline CD4 count (cells/µL)						
≥350	1		0.31	1		0.60
200-350	0.97	0.82, 1.14		0.92	0.78, 1.09	
<200	1.07	0.92, 1.25		0.98	0.83, 1.15	
Type of initial cART regimen						
NNRTI	1		0.42	1		0.53
PI	1.07	0.95, 1.21		1.05	0.93, 1.19	
Other	1.16	0.87, 1.55		1.15	0.86, 1.55	

[a] Each factor considered in separate univariable models then all factors in a single multivariable model; [b] likelihood ratio test; [c] adjusted for all factors listed in the table; denominators are provided in Table 6.6; RR= risk ratio; aRR= adjusted risk ratio; NNRTI= Non-Nucleoside Reverse Transcriptase Inhibitors; PI= Protease Inhibitors.

Table 6.8: Associations of gender/sexual orientation, calendar year of cART initiation and other factors at baseline with virological non-suppression 24-30 months after cART initiation - Strategy B (missing=excluded)

Factor [a]	Unadjusted			Adjusted		
	RR	95% CI	P-value [b]	aRR [c]	95% CI	P-value [b]
Gender/ sexual orientation						
MSW vs. MSM	1.54	1.11, 2.15	<.0001	1.63	1.17, 2.27	<.0001
Women vs. MSM	1.96	1.49, 2.57		1.90	1.43, 2.51	
Women vs. MSW	1.27	0.92, 1.76		1.16	0.84, 1.61	
Calendar year of cART initiation						
Per year	0.89	0.86, 0.92	<.0001	0.89	0.86, 0.93	<.0001
Age						
Per 10 years	0.73	0.63, 0.86	<.0001	0.81	0.70, 0.93	0.0022
Baseline VL (copies/ mL)						
<10000	1		0.19	1		0.44
10000-99999	0.84	0.57, 1.24		0.87	0.60, 1.25	
≥100000	1.08	0.75, 1.55		1.03	0.71, 1.48	
Baseline CD4 count (cells/µL)						
≥350	1		0.018	1		0.035
200-350	0.74	0.52, 1.04		0.63	0.45, 0.88	
<200	1.11	0.83, 1.50		0.75	0.55, 1.02	
Type of initial cART regimen						
NNRTI	1		0.12	1		0.082
PI	1.30	1.01, 1.67		1.32	1.04, 1.69	
Other	1.14	0.59, 2.22		1.12	0.59, 2.14	

[a] Each factor considered in separate univariable models then all factors in a single multivariable model; [b] likelihood ratio test; [c] adjusted for all factors listed in the table; denominators are provided in Table 6.6; RR= risk ratio; aRR= adjusted risk ratio; NNRTI= Non-Nucleoside Reverse Transcriptase Inhibitors; PI= Protease Inhibitors.

Table 6.9: Associations of gender/sexual orientation, calendar year of cART initiation and other factors at baseline with virological non-suppression 24-30 months after cART initiation - Strategy C (on cART)

Factor [a]	Unadjusted			Adjusted		
	RR	95% CI	P-value [b]	aRR [c]	95% CI	P-value [b]
Gender/ sexual orientation						
MSW vs. MSM	2.13	1.45, 3.11	<.0001	1.98	1.34, 2.91	0.0004
Women vs. MSM	2.07	1.46, 2.95		1.83	1.28, 2.61	
Women vs. MSW	0.98	0.67, 1.42		0.92	0.63, 1.35	
Calendar year of cART initiation						
Per year	0.90	0.86, 0.94	<.0001	0.93	0.88, 0.97	0.0023
Age						
Per 10 years	0.81	0.67, 0.97	0.019	0.85	0.71, 1.02	0.064
Baseline VL (copies/ mL)						
<10000	1		0.0040	1		0.049
10000-99999	1.07	0.60, 1.91		1.03	0.58, 1.82	
≥100000	1.78	1.04, 3.04		1.53	0.88, 2.67	
Baseline CD4 count (cells/µL)						
≥350	1		<.0001	1		0.067
200-350	1.60	0.93, 2.76		1.32	0.76, 2.29	
<200	2.77	1.68, 4.55		1.71	1.01, 2.89	
Type of initial cART regimen						
NNRTI	1		0.70	1		0.47
PI	1.14	0.84, 1.55		1.21	0.89, 1.65	
Other	0.99	0.42, 2.34		1.06	0.45, 2.49	

[a] Each factor considered in separate univariable models then all factors in a single multivariable model; [b] likelihood ratio test; [c] adjusted for all factors listed in the table; denominators are provided in Table 6.6; RR= risk ratio; aRR= adjusted risk ratio; NNRTI= Non-Nucleoside Reverse Transcriptase Inhibitors; PI= Protease Inhibitors.

6.4.2.4 *Interaction between gender/sexual orientation and calendar year of cART initiation*

Table 6.10 shows the tests for interaction between calendar time and gender/sexual orientation. Among all gender/sexual orientation groups, there was evidence of reductions in risk of virological non-suppression 24 months after cART initiation under strategy B; however, there was no evidence of an increasing trend under strategy A, and only among MSM under strategy C. However, there was no evidence of differences in relative change in virological non-suppression per calendar year of cART initiation by gender/sexual orientation in any of the three analysis strategies.

Table 6.10: Associations of the interaction between gender/sexual orientation and calendar year of cART initiation with virological non-suppression at 24 months

		Strategy A (missing=failure)			Strategy B (missing=excluded)			Strategy C (on cART)		
		aRR [a]	95% CI	P-value[b]	aRR [a]	95% CI	P-value[b]	aRR [a]	95% CI	P-value[b]
Relative change per calendar year of cART initiation	MSM	1.00	0.98, 1.03	0.51	0.87	0.82, 0.93	0.36	0.90	0.83, 0.98	0.56
	MSW	0.98	0.94, 1.01		0.88	0.81, 0.96		0.92	0.84, 1.01	
	Women	0.99	0.97, 1.02		0.93	0.87, 0.99		0.96	0.88, 1.04	

[a] Adjusted for age, baseline VL and CD4 count, initial cART regimen; [b] likelihood ratio test; aRR= adjusted risk ratio.

6.4.3 **Treatment disruptions**

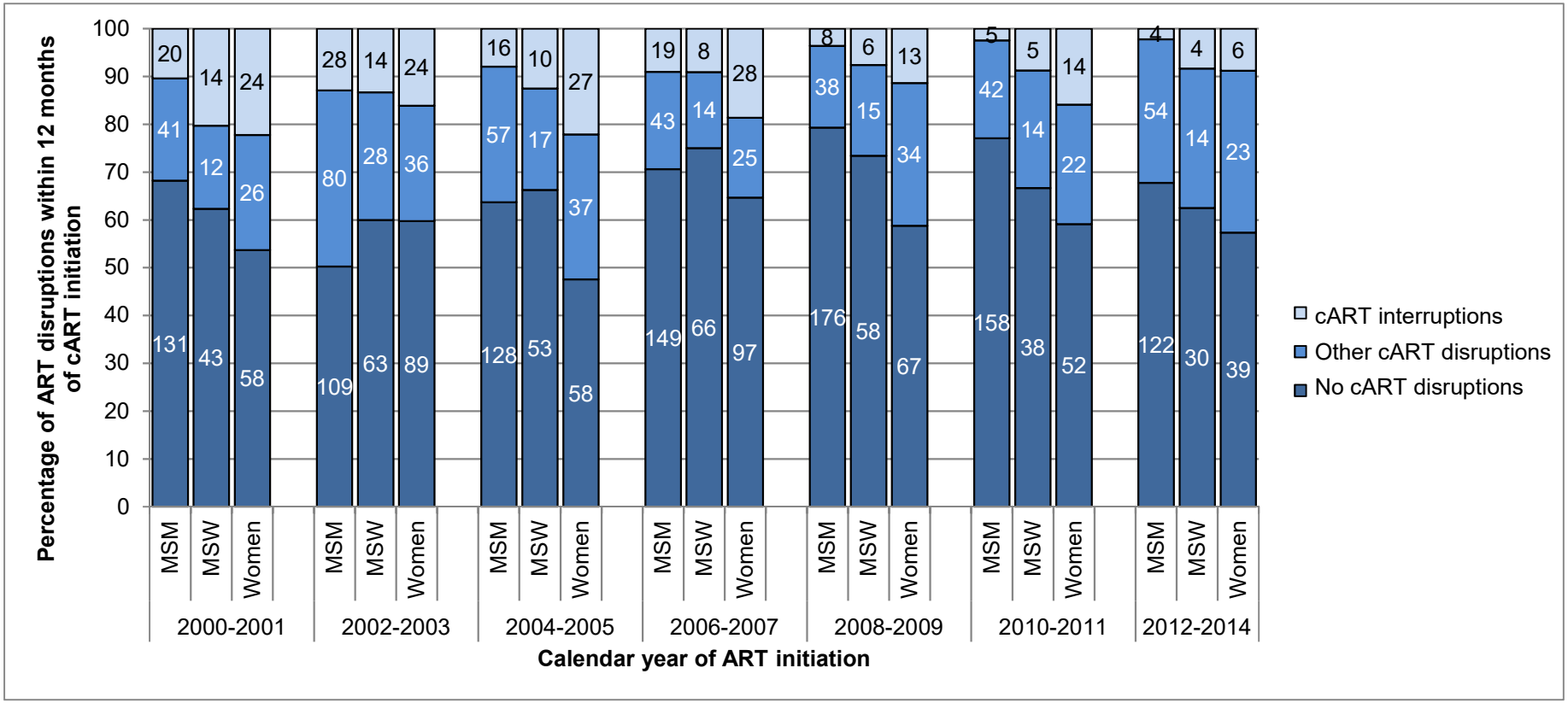
The prevalence of treatment disruptions was considered among the 2753 individuals who had initiated cART between January 2000 and March 2014 aged over 18 years with sexually acquired HIV. Over the first 12 months of cART: 297 (11%) interrupted cART (stopped all ARV drugs for over seven consecutive days); 672 (24%) had other disruptions (of the individuals who had not interrupted cART); and the remaining 1784 (65%) had no cART disruptions (on the same cART regimen for the 12-month period).

Both cART interruption and cART disruption were associated with a greater prevalence of virological non-suppression. Among individuals who interrupted cART within 12 months of cART initiation, 70% had virological non-suppression compared to 13% of those who did not stop (p<0.0001). In addition, 30% of individuals who did not interrupt but disrupted treatment had virological non-suppression compared to 11% of those who had no disruptions (p<0.0001).

6.4.3.1 ***Prevalence of cART disruptions during the first 12 months of cART initiation by calendar year of cART initiation and gender/sexual orientation***

In Figure 6.5 the percentage of MSM, MSW and women who interrupted cART, who had other cART disruptions, or who had no treatment disruptions are shown over calendar year of cART initiation. The percentage who interrupted their cART regimen before 12 months tended to decrease with more recent year of cART initiation in all gender/sexual orientation groups. However, there remained a consistently higher percentage of women who had interrupted cART compared to MSM (2000-01: 22% vs. 10%; 2012-14: 9% vs. 2%), while differences between MSW and MSM tended to be smaller.

Figure 6.5: The percentage with any cART disruptions during the first 12 months of cART initiation by gender/sexual orientation over calendar year of cART initiation



Numbers on each bar represent the number of individuals in that category

6.4.3.2 *The associations of gender-sexual orientation and calendar year of cART initiation with cART interruptions and disruptions during the first 12 months of cART initiation*

A higher risk of cART interruption was seen among MSW compared to MSM, and among women compared to either MSM or MSW in both unadjusted and adjusted analyses (Table 6.11). Earlier calendar years of cART initiation, younger age, lower baseline VL, and higher baseline CD4 count were associated with higher risk of cART interruption. There was no evidence of an association with initial cART regimen.

Also shown in Table 6.11 are associations with either form of treatment disruption: cART interruptions or cART switches within 12 months of initiation. Women had an increased risk of treatment disruption compared to either MSW or MSM, although there were no differences between MSW and MSM. The risk of any treatment disruption decreased over calendar year of cART initiation, but the effect size was smaller than that seen when considering cART interruption as an outcome alone. The associations between the other covariates and cART disruption were similar to the cART interruption analysis, except that baseline VL ≥100000 copies/mL compared to <10000 copies/mL, and PI- and other-based initial regimen compared to NNRTI-based were associated with a higher risk of cART disruption.

Table 6.11: Associations of gender/sexual orientation, calendar year of cART initiation and other factors at baseline with cART interruption [a] or cART disruption [b] during the first 12 months of cART initiation

Factors [c]	cART interruption						cART disruption					
	RR	95% CI	P-value[d]	aRR [e]	95% CI	P-value[d]	RR	95% CI	P-value[d]	aRR [e]	95% CI	P-value[d]
Gender/ sexual orientation												
MSW vs. MSM	1.66	1.22, 2.24	<.0001	1.78	1.31, 2.42	<.0001	1.04	0.91, 1.20	<.0001	1.08	0.93, 1.24	<.0001
Women vs. MSM	2.43	1.91, 3.10		2.36	1.83, 3.03		1.33	1.19, 1.49		1.34	1.20, 1.51	
Women vs. MSW	1.47	1.11, 1.94		1.32	1.00, 1.75		1.28	1.11, 1.48		1.25	1.08, 1.45	
Calendar year of cART initiation												
Per year	0.91	0.88, 0.93	<.0001	0.90	0.88, 0.93	<.0001	0.97	0.96, 0.98	<.0001	0.97	0.96, 0.98	<.0001
Age												
Per 10 years	0.77	0.67, 0.88	<.0001	0.86	0.76, 0.98	0.017	0.92	0.87, 0.98	0.0055	0.95	0.90, 1.01	0.079
Baseline VL (copies/mL)												
<10000	1		0.0054	1		0.065	1		0.0057	1		0.0080
10000-99999	0.74	0.57, 0.95		0.85	0.65, 1.09		0.90	0.79, 1.03		0.96	0.83, 1.09	
≥100000	0.66	0.51, 0.85		0.74	0.57, 0.95		1.10	0.98, 1.24		1.15	1.02, 1.30	
Baseline CD4 count (cells/μL)												
≥350	1		0.0004	1		<.0001	1		0.0005	1		0.0001
200-350	0.56	0.41, 0.77		0.46	0.34, 0.63		0.78	0.67, 0.90		0.73	0.63, 0.84	
<200	0.87	0.68, 1.12		0.57	0.44, 0.74		0.97	0.85, 1.09		0.83	0.73, 0.95	
Type of initial cART regimen												
NNRTI	1		0.90	1		0.69	1		0.022	1		0.015
PI	1.05	0.84, 1.31		1.10	0.88, 1.36		1.11	1.00, 1.23		1.11	1.00, 1.23	
Other	1.07	0.65, 1.76		1.11	0.67, 1.84		1.31	1.07, 1.61		1.35	1.10, 1.66	

[a] cART interruption= stopping all ARVs for greater than seven consecutive days; [b] cART disruption= stopping all ARVs for greater than seven consecutive days or switching cART regimen for reasons other than simplification; [c] each factor considered in separate univariable models then all factors in a single multivariable model; [d] likelihood ratio test; [e] adjusted for all factors listed in the table; RR= Risk Ratio; aRR= adjusted Risk Ratio; NNRTI= Non-Nucleoside Reverse Transcriptase Inhibitors; PI= Protease Inhibitors.

6.4.3.3 *Test for interaction between gender/sexual orientation and calendar year of cART initiation*

There was an estimated average 14% reduction in the risk of interrupting cART within the first 12 months per year later of cART initiation among MSM, compared to 9% and 6% among MSW and women, respectively (Table 6.12). A test for interaction suggested the trend was greater among MSM compared to MSW, and particularly compared to women (p=0.029). This indicates that, while in more recent years of cART initiation all three groups were less likely to discontinue their cART regimen, the reduction in risk over time was greatest for MSM. A similar pattern was apparent for risk of cART disruptions, although trends were considerably weaker in all gender/sexual orientation groups (Table 6.12).

Table 6.12: Associations of the interaction between gender/sexual orientation and calendar year of cART initiation with cART interruptions and disruptions during the first 12 months of cART initiation

		cART interruption			cART disruption		
		aRR [a]	95% CI	P-value[b]	aRR [a]	95% CI	P-value[b]
Relative change per calendar year of cART initiation	MSM	0.86	0.83, 0.90	0.029	0.96	0.94, 0.98	0.078
	MSW	0.91	0.85, 0.98		0.98	0.94, 1.01	
	Women	0.94	0.90, 0.98		0.99	0.97, 1.01	

[a] For age, baseline CD4 count and VL, and third drug in initial ART regimen; [b] likelihood ratio test for interaction term; aRR= adjusted risk ratio.

6.4.3.4 *cART disruptions during the first 12 months of cART initiation as a mediating factor for associations between gender/sexual orientation and virological non-suppression at 12 months*

An analysis considering virological non-suppression at 12 months as the outcome and cART disruptions (cART interruptions vs. other cART disruptions vs. no disruptions) as a mediating factor was performed. The RRs for the associations between the covariates and virological non-suppression are displayed in Table 6.13. The first and second columns were equivalent to those in Table 6.2 for the main analysis of virological non-suppression at 12 months, but were included here for comparison. Additionally, a univariable model for the association between cART disruptions and virological non-suppression was assessed: cART switches and cART interruptions were associated with 1.5 times and 6.6 times the risk of virological non-suppression compared to no disruptions, respectively.

Following adjustment for cART disruptions the adjusted RRs in column 2 of Table 6.13 were attenuated towards one by 19% and 49% for MSW and women compared to

MSM, respectively, however, the risk of virological non-suppression at 12 months remained higher among MSW and women. There was also an attenuation of the association of calendar year of cART initiation, age, baseline VL, and baseline CD4 count with virological non-suppression; however, associations with type of initial cART regimen were not reduced. cART interruptions and other cART disruptions remained very strongly associated with a greater risk of virological non-suppression compared to no treatment disruptions in this multivariable model.

Table 6.13: Associations of gender/sexual orientation, calendar year of cART initiation and other factors at baseline with virological non-suppression at 12-18 months after cART initiation and additional adjustment for cART disruptions [a] [b]

Factors	Unadjusted [c]			Adjusted [d]			Adjusted additionally for cART disruptions [e]		
	RR	95% CI	P-value[f]	aRR	95% CI	P-value[f]	aRR	95% CI	P-value[f]
Gender/ sexual orientation									
MSW vs. MSM	1.45	1.06, 1.96	<.0001	1.60	1.17, 2.20	<.0001	1.41	1.04, 1.91	0.019
Women vs. MSM	1.93	1.51, 2.47		1.87	1.45, 2.43		1.38	1.07, 1.77	
Women vs. MSW	1.34	0.99, 1.80		1.17	0.86, 1.58		0.98	0.73, 1.31	
Calendar year of cART initiation									
Per year	0.93	0.90, 0.96	<.0001	0.92	0.89, 0.95	<.0001	0.96	0.92, 0.99	0.0070
Age									
Per 10 years	0.77	0.67, 0.88	<.0001	0.84	0.74, 0.96	0.0095	0.88	0.77, 1.00	0.039
Baseline VL (copies/ mL)									
<10000	1		0.0024	1		0.0028	1		0.013
10000-99999	0.62	0.44, 0.86		0.67	0.48, 0.92		0.76	0.57, 1.02	
≥100000	0.90	0.67, 1.22		1.00	0.73, 1.37		1.09	0.81, 1.46	
Baseline CD4 count (cells/µL)									
≥350	1		0.96	1		0.093	1		0.52
200-350	0.97	0.72, 1.29		0.83	0.63, 1.11		1.13	0.87, 1.46	
<200	1.00	0.76, 1.32		0.71	0.53, 0.96		0.99	0.74, 1.33	
Type of initial cART regimen									
NNRTI	1		0.0009	1		0.0005	1		0.0004
PI	1.51	1.19, 1.91		1.52	1.21, 1.91		1.49	1.20, 1.85	
Other	1.80	1.13, 2.88		1.73	1.10, 2.73		1.73	1.12, 2.67	
cART disruptions within 12 months of cART initiation									
None	1		<.0001	-	-	-	1		<.0001
Switched	1.54	1.16, 2.05		-	-	-	1.42	1.07, 1.88	
Interrupted	6.57	5.29, 8.17		-	-	-	5.33	4.19, 6.79	

[a] ART disruption: interrupted ART (stopping all ARVs for greater than seven consecutive days); switched ART (if not stopped then switched any ARV for reasons other than simplification); or no disruptions; [b] using analysis strategy B: missing VL at 12 months= excluded; [c] each factor considered in separate univariable models; [d] adjusted for all factors listed in the table except ART disruptions; [e] adjusted for all factors listed in the table including ART adherence; [f] likelihood ratio test; RR= Risk Ratio; aRR= adjusted Risk Ratio; NNRTI= Non-Nucleoside Reverse Transcriptase Inhibitors; PI= Protease Inhibitors.

6.4.3.5 *Reasons for cART disruptions by gender/sexual orientation*

Of the 969 individuals who had disrupted their cART regimen within 12 months of cART initiation, 943 (97%) had a clinician-completed reason recorded for stopping at least one ARV. The reasons are summarised in Table 6.14. The frequencies sum to over 943 since 370 (39%) individuals had different reasons recorded when stopping more than one ARV (262 two ARVs; 81 three ARVs; 25 four ARVs; two had five ARVs), leading to 1450 ARV switches over the first 12 months of cART.

Toxicity was the main reason for stopping an ARV (39%) followed by rationalisation (14%) and patient choice (12%). Rationalisation usually means simplification of an individual's cART regimen, for example changing to a single tablet once a day regimen.

There were differences in the reasons given for cART disruptions by gender/sexual orientation group. For example, of all the stopping reasons and treatment failure reasons were more prevalent for MSW and toxicity reasons were more prevalent among MSM. CNS effects and rash were in the top three toxicity reasons for treatment disruption for all three gender/sexual orientation groups; however, diarrhoea, renal problems, and nausea were more prevalent among MSM, MSW, and women, respectively. Among MSW and women "other reasons" and not having reasons recorded in their notes were more common than among MSM.

Table 6.14: Reasons for disruption of cART regimen during the first 12 months of cART initiation by gender/sexual orientation

Reason	Overall		MSM		MSW		Women	
	N	% [a]	N	% [a]	N	% [a]	N	% [a]
Treatment failure	**82**	**5.7**	**30**	**4.4**	**24**	**9.1**	**28**	**5.5**
Virological failure	58	4.0	23	3.4	16	6.1	19	3.7
CD4 count failure	2	0.1	1	0.1	1	0.4	0	0
Increased resistance	22	1.5	6	0.9	7	2.7	9	1.8
Study end point or change	**50**	**3.4**	**41**	**6.1**	**4**	**1.5**	**5**	**1.0**
Toxicity (any)	**558**	**38.5**	**294**	**43.4**	**80**	**30.4**	**184**	**36.1**
CNS effects / insomnia	147	10.1	90	13.3	24	9.1	33	6.5
Rash	71	4.9	34	5.0	14	5.3	23	4.5
Nausea / vomiting	58	4.0	25	3.7	5	1.9	28	5.5
Diarrhoea	56	3.9	42	6.2	3	1.1	11	2.2
Anaemia	52	3.6	24	3.5	8	3.0	20	3.9
Renal problem	40	2.8	17	2.5	10	3.8	13	2.5
Abnormal LFTs	31	2.1	13	1.9	4	1.5	14	2.7
Peripheral neuropathy	24	1.7	13	1.9	3	1.1	8	1.6
Allergic reaction	18	1.2	9	1.3	2	0.8	7	1.4
Gastrointestinal side effects /intolerance	11	0.8	2	0.3	2	0.8	7	1.4
Malaise /fatigue	8	0.6	5	0.7	0	0.0	3	0.6
Skin problems	8	0.6	2	0.3	1	0.4	5	1.0
Lipid abnormality	7	0.5	7	1.0	0	0.0	0	0
Lipodystrophy	6	0.4	3	0.4	1	0.4	2	0.4
Abdominal pain	6	0.4	2	0.3	0	0.0	4	0.8
Other toxicity	15	1.0	6	0.9	3	1.1	6	1.2
Pregnancy	**42**	**2.9**	**0**	**0.0**	**0**	**0.0**	**42**	**8.2**
Rationalization	**202**	**13.9**	**105**	**15.5**	**37**	**14.1**	**60**	**12.0**
Patient choice	**180**	**12.4**	**86**	**12.9**	**32**	**12.2**	**62**	**12.2**
Death	**17**	**1.2**	**4**	**0.6**	**10**	**3.8**	**3**	**0.6**
Other reasons	**167**	**11.5**	**64**	**9.5**	**40**	**15.2**	**63**	**12.4**
Other	123	8.5	47	6.9	29	11.0	47	9.2
Poor compliance	17	1.2	8	1.2	5	1.9	4	0.8
Drug interaction	24	1.7	8	1.2	6	2.3	10	2.0
Following a TDM result	3	0.2	1	0.1	0	0.0	2	0.4
Not recorded	**152**	**10.5**	**53**	**7.8**	**36**	**13.7**	**63**	**12.4**

[a] Percentages may not sum to 100 due to rounding; other toxicity includes: intolerance, headache, pancreatitis, diabetes, myositis and raised amylases; CNS= central nervous system; LFTs= liver function tests; TDM= therapeutic drug monitoring.

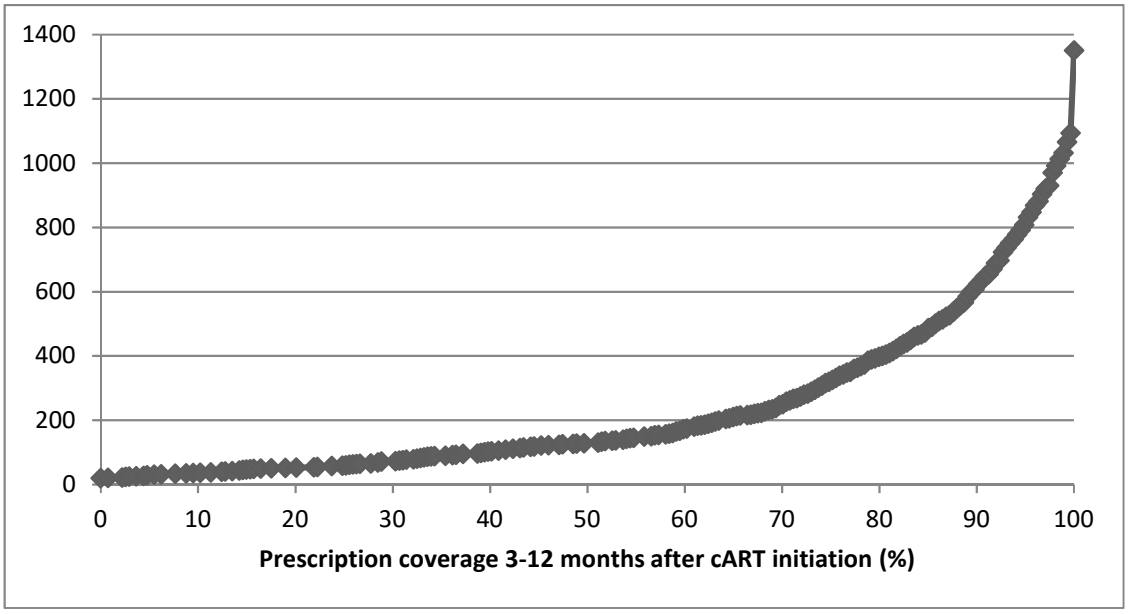
6.4.4 **Treatment non-adherence at 12 months**

6.4.4.1 ***Prevalence of treatment non-adherence between three and 12 months after cART initiation***

Of the 2753 individuals initiating cART between January 2000 and March 2014 aged over 18 years with sexually acquired HIV, 2644 had any prescription data over follow-up. Of these, 1351 (51%) had a prescription recorded within seven days of the date of cART initiation and at least one additional prescription between one and three months after cART initiation, and were therefore included: 716 (53%) MSM; 251 (19%) MSW; 384 (28%) women.

The distribution of percentage cART coverage is displayed in Figure 6.6. There were 257 (19%) individuals with 100% adherence, 486 (36%) with 90-99% prescription coverage, 211 (16%) with 80-89%, 225 (17%) with 60-79%, and the remaining 172 (13%) had <60% adherence.

Figure 6.6: Cumulative frequency distribution of the prescription based treatment adherence measure [a]



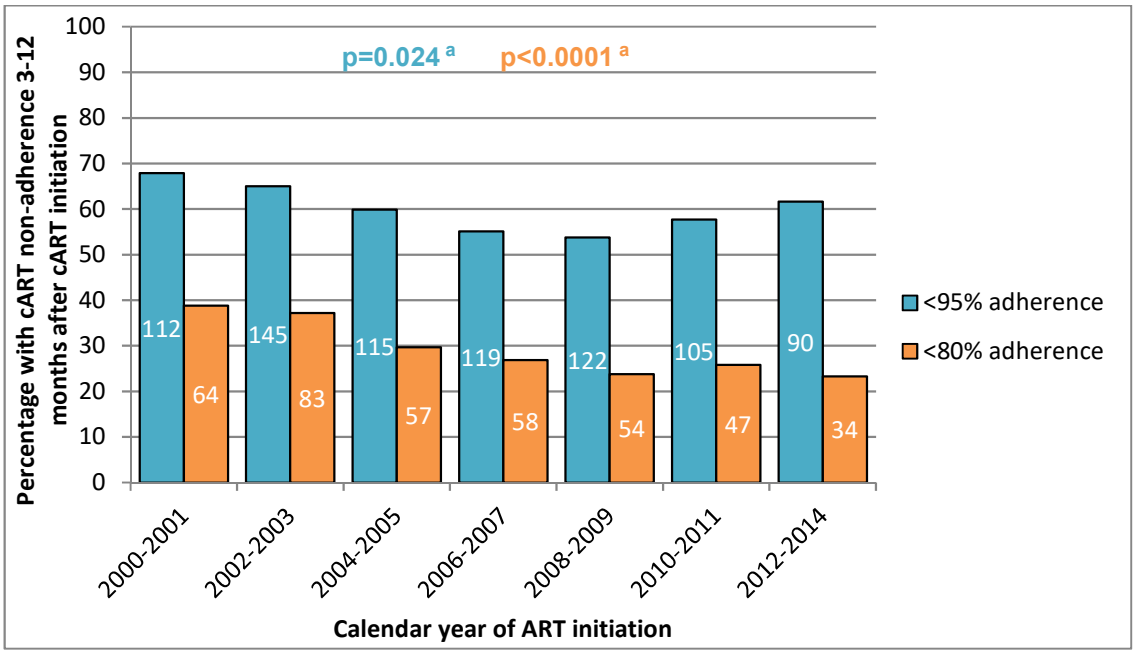
[a] N=1351 individuals who had a prescription for cART recorded within a week of the date recorded that they first initiated cART and who had at least one further cART prescription between one and three months after cART initiation.

Of the 1351 individuals, 808 (60%) and 397 (29%) had <95% and <80% prescription coverage between three and 12 months after cART initiation, respectively.

Among individuals with <95% adherence, 16% had a VL >50 copies/mL at 12 months after cART initiation compared to 12% of individuals with ≥95% adherence (p=0.025). Likewise, of individuals with <80% adherence, 24% had VL >50 copies/mL compared to 11% of individuals with ≥80% adherence (p<0.0001).

The prevalence of <95% cART adherence between three and 12 months after cART initiation fell from 2000/2001 to 2008/2009, but then rose again in the more recent periods. For <80% adherence, the prevalence tended to decrease over the whole period (Figure 6.7).

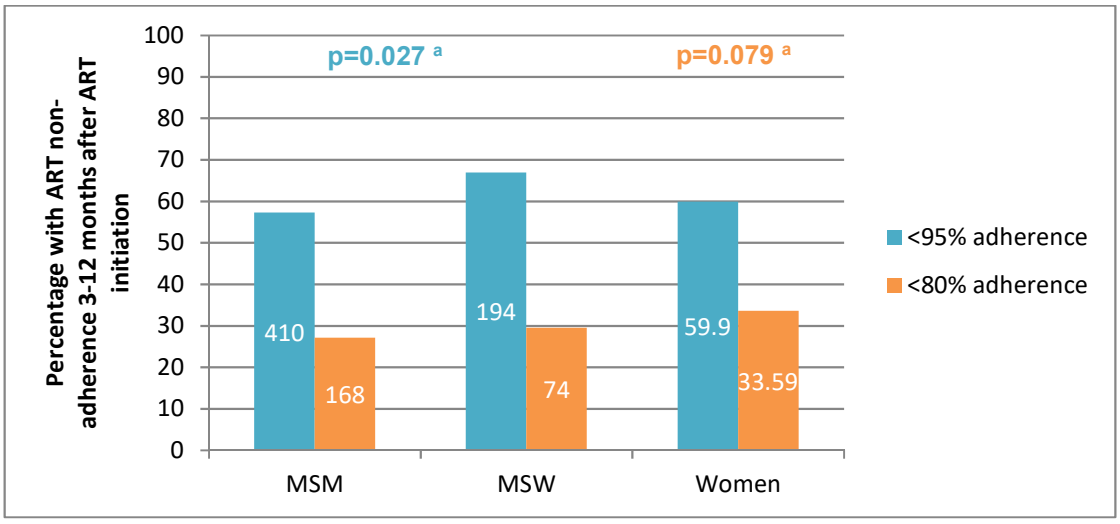
Figure 6.7: Percentage with cART non-adherence between three and 12 months after cART initiation by calendar year of cART initiation



[a] Cochran-Armitage test for trend; numbers on each bar represent the number of individuals in that category.

Overall a lower percentage of MSM had <95% cART adherence compared to women and MSW in particular (Figure 6.8). Similarly, a lower percentage of MSM had <80% cART adherence compared to MSW and women.

Figure 6.8: Percentage with cART non-adherence between three and 12 months after cART initiation by calendar year of cART initiation



[a] Chi-squared test; numbers on each bar represent the number of individuals in that category.

6.4.4.2 *The association between gender-sexual orientation, calendar year of cART initiation and cART non-adherence between three and 12 months after cART initiation*

The RRs for the associations between the covariates and <95% adherence are shown in Table 6.15. In unadjusted analyses the factors associated with a higher risk of <95% adherence were: MSW compared to MSM or women; less recent calendar year of cART initiation; an “other-based” initial cART regimen compared to NNRTI-based. There were no significant differences between women and either MSM or MSM, by age, or by baseline VL or CD4 count. In the multivariable model the same factors remained associated with a higher risk of <95% adherence.

Table 6.15 also shows the RRs for the associations between the covariates and <80% adherence. In contrast to the analysis of <95% as an endpoint, women had a higher unadjusted risk of non-adherence compared to MSM. Individuals who initiated cART in earlier years had a higher risk of non-adherence. In adjusted analyses, calendar year of cART initiation was the only factor which remained associated with <80% adherence: a 5% reduction in the adjusted risk of <80% cART adherence per year more recently that cART was initiated.

Table 6.15: Associations of gender/sexual orientation, calendar year of cART initiation and other factors at baseline with cART non-adherence between three and 12 months after cART initiation

Factors [a]	<95% cART adherence				<80% cART adherence			
	RR (95% CI)	P-value[b]	aRR (95% CI) [c]	P-value[b]	RR (95% CI)	P-value[b]	aRR (95% CI) [c]	P-value[b]
Gender/ sexual orientation								
MSW vs. MSM	1.17 (1.05, 1.30)	0.023	1.16 (1.04, 1.30)	0.031	1.09 (0.87, 1.36)	0.086	1.06 (0.84, 1.33)	0.25
Women vs. MSM	1.05 (0.94, 1.16)		1.03 (0.92, 1.15)		1.24 (1.03, 1.49)		1.18 (0.97, 1.44)	
Women vs. MSW	0.89 (0.79, 1.01)		0.88 (0.78, 1.00)		1.14 (0.90, 1.14)		1.12 (0.88, 1.42)	
Calendar year of cART initiation								
Per year	0.99 (0.98, 1.00)	0.022	0.99 (0.98, 1.00)	0.052	0.95 (0.93, 0.98)	<.0001	0.95 (0.93, 0.98)	<.0001
Age								
Per 10 years	0.97 (0.93, 1.02)	0.25	0.97 (0.93, 1.02)	0.31	0.92 (0.84, 1.02)	0.093	0.95 (0.87, 1.05)	0.34
Baseline VL (copies/mL)								
<10000	1	0.24	1	0.51	1	0.87	1	0.77
10000-99999	0.94 (0.82, 1.06)		0.96 (0.84, 1.09)		0.94 (0.74, 1.19)		0.99 (0.78, 1.25)	
≥100000	1.02 (0.90, 1.15)		1.02 (0.90, 1.15)		0.95 (0.76, 1.19)		0.93 (0.74, 1.18)	
Baseline CD4 count (cells/µL)								
≥350	1	0.42	1	0.96	1	0.36	1	0.69
200-350	1.01 (0.89, 1.14)		0.98 (0.87, 1.11)		1.01 (0.81, 1.28)		0.91 (0.72, 1.15)	
<200	1.07 (0.95, 1.19)		1.00 (0.88, 1.13)		1.14 (0.92, 1.41)		0.97 (0.77, 1.23)	
Type of initial cART regimen								
NNRTI	1	0.13	1	0.097	1	0.56	1	0.45
PI	1.04 (0.96, 1.14)		1.05 (0.96, 1.15)		0.99 (0.83, 1.17)		1.00 (0.84, 1.18)	
Other	1.23 (1.02, 1.50)		1.26 (1.04, 1.53)		1.26 (0.85, 1.87)		1.34 (0.89, 2.03)	

[a] Each factor considered in separate univariable models then all factors in a single multivariable model; [b] likelihood ratio test; [c] adjusted for all factors listed in the table; RR= risk ratio; aRR= adjusted risk ratio; NNRTI= Non-Nucleoside Reverse Transcriptase Inhibitors; PI= Protease Inhibitors.

6.4.4.3 *Test for interaction between gender/sexual orientation and calendar year of cART initiation*

Among MSM, the adjusted risk of <95% adherence decreased by 2% per year later that cART was initiated, and the risk of <80% adherence decreased by 7% per year. However, there was no evidence of an increasing trend in adherence over time among MSW or women (Table 6.16). Despite these differences there was no evidence that the reductions in risk of cART non-adherence by calendar year of cART initiation differed by gender/sexual orientation (p=0.26 and p=0.13).

Table 6.16: Associations of the interaction between gender/sexual orientation and calendar year of cART initiation with cART non-adherence between three and 12 months after cART initiation

		<95% adherence			<80% adherence		
		aRR [a]	95% CI	P-value[b]	aRR [a]	95% CI	P-value[b]
Relative change per calendar year of cART initiation	MSM	0.98	0.96, 1.00	0.26	0.93	0.90, 0.96	0.13
	MSW	1.00	0.98, 1.02		0.97	0.92, 1.02	
	Women	1.00	0.97, 1.02		0.98	0.94, 1.02	

[a] For age, baseline CD4 count and VL, and third drug in initial cART regimen; [b] likelihood ratio test; aRR= adjusted risk ratio.

6.4.4.4 *Adherence as a mediating factor for the association between gender/sexual orientation and virological non-suppression at 12 months*

An analysis considering virological non-suppression at 12 months as the outcome and adherence as a mediating factor was performed. There were 1615 individuals that met the inclusion criteria for strategy B (missing VL at 12 months=excluded). Of these, 1087 additionally had at least one prescription recorded within seven days of cART initiation and another recorded between one to three months after initiation. A total of 592 (54%) were MSM, 195 (18%) were MSW, and 300 (28%) were women.

The results of the unadjusted and adjusted modified Poisson regression models for virological non-suppression are displayed in Table 6.17. These results are similar to that in the main analysis. In addition, there was evidence of a 17% higher unadjusted risk of virological non-suppression at 12 months per 10% additional prescription coverage between three and 12 months after cART initiation.

Additionally, adjustment for non-adherence attenuated the association between gender/sexual orientation and virological non-suppression by 9% and 19% for MSW and women compared to MSM, respectively (Table 6.17). This was likely a result of the increasing trend over time in adherence among MSM compared to the lack of evidence of a trend among MSW and women.

Table 6.17: Associations of gender/sexual orientation, calendar year of cART initiation and other factors at baseline with virological non-suppression at 12 months with additional adjustment for cART non-adherence

Factors [a]	Unadjusted			Adjusted			Adjusted additionally for non-adherence		
	RR	95% CI	P-value [b]	aRR [c]	95% CI	P-value [b]	aRR [d]	95% CI	P-value [b]
Gender/ sexual orientation									
MSW vs. MSM	1.62	1.08, 2.43	0.0002	1.68	1.11, 2.55	0.0007	1.59	1.06, 2.40	0.0035
Women vs. MSM	2.04	1.46, 2.85		1.98	1.39, 2.81		1.79	1.26, 2.53	
Women vs. MSM	1.26	0.85, 1.87		1.17	0.79, 1.75		1.12	0.76, 1.66	
Calendar year of cART initiation									
Per year	0.93	0.89, 0.97	0.0005	0.93	0.89, 0.97	0.0008	0.94	0.90, 0.99	0.013
Age									
Per 10 years	0.85	0.71, 1.02	0.065	0.93	0.77, 1.10	0.38	0.94	0.80, 1.12	0.52
Baseline VL (copies/mL)									
<10000	1		0.075	1		0.17	1		0.14
10000-99999	0.68	0.43, 1.08		0.75	0.47, 1.19		0.80	0.51, 1.25	
≥100000	0.97	0.64, 1.48		1.02	0.66, 1.58		1.12	0.60, 1.34	
Baseline CD4 count (cells/μL)									
≥350	1		0.32	1		0.71	1		0.83
200-350	1.02	0.67, 1.55		0.84	0.55, 1.27		0.90	0.60, 1.34	
<200	1.28	0.87, 1.89		0.86	0.57, 1.32		0.98	0.65, 1.47	
Type of initial cART regimen									
NNRTI	1		0.031	1		0.021	1		0.024
PI	1.43	1.04, 1.95		1.45	1.07, 1.98		1.43	1.06, 1.93	
Other	2.14	1.11, 4.11		2.08	1.08, 4.00		1.99	1.10, 3.60	
Adherence									
Per additional 10%	0.83	0.80, 0.86	<.0001	-		-	0.85	0.81, 0.89	<.0001

[a] Each factor considered in separate univariable models then all factors in a single multivariable model; [b] likelihood ratio test; [c] adjusted for all factors listed in the table except cART adherence; [d] adjusted for all factors listed in the table including cART adherence; RR= risk ratio; aRR= adjusted risk ratio; NNRTI= Non-Nucleoside Reverse Transcriptase Inhibitors; PI= Protease Inhibitors.

6.4.5 **Sensitivity analyses**

6.4.5.1 ***Virological non-suppression at 12 months***

Viral load cut-off changed to 200 copies/mL (instead of 50 copies/mL)

There were 517/1971 (26%), 161/1615 (10%), and 91/1522 (6%) individuals with VL >200 copies/mL at 12 months under analysis strategies A, B, and C, respectively. Using this definition of virological non-suppression, the results were comparable to those in the main analysis (Table 6.18 and Table 6.19).

Individuals not excluded if missing baseline VL and CD4 count (complete case analysis)

In the main analysis, 754 (12%) individuals were excluded due to missing baseline VL or CD4 count. When these individuals were included, there were 1129/2710 (42%), 355/1936 (18%), and 249/1801 (14%) individuals with virological non-suppression using analysis strategies A, B, and C, respectively. The prevalence of virological non-suppression was substantially higher for analysis strategy A compared to the main analysis (42% vs 31%). However, the RRs found in these analyses were similar to those in the main analysis, which suggested that the exclusion of these individuals had not biased the results (Table 6.18 and Table 6.19).

Virological non-suppression defined using a VL measurement between six and 18 months after cART initiation

There were 447/1971 (23%), 280/1804 (16%), and 204/1711 (12%) individuals with virological non-suppression at 12 months under strategies A, B, and C, respectively. The prevalence of virological non-suppression was substantially lower for analysis strategy A compared to the main analysis (23% vs 31%), but equivalent to the main analysis under the other two analysis strategies. Furthermore, the RRs in this sensitivity analysis were largely consistent with those of the main analysis (Table 6.18 and Table 6.19). One exception to this was that, unlike in the main analysis, increasing calendar time was associated with lower risk of virological non-suppression under strategy A as well as the other strategies. Additionally, contrasting to the main analysis, for strategy C there was no evidence of a higher adjusted risk of virological non-suppression among women compared to MSM.

Table 6.18: Associations of gender/sexual orientation and calendar year of cART initiation with virological non-suppression 12-18 months after cART initiation – sensitivity analyses

Factors		Strategy A (missing=failure)			Strategy B (missing=excluded)			Strategy C (on cART)		
		aRR [a]	95% CI	P-value[b]	aRR [a]	95% CI	P-value[b]	aRR [a]	95% CI	P-value[b]
Viral load cut-off changed to 200 copies/mL (instead of 50 copies/mL)										
Gender/ sexual orientation	MSW vs. MSM	1.53	1.26, 1.87	<.0001	2.90	1.88, 4.47	<.0001	3.95	2.23, 6.98	<.0001
	Women vs. MSW	1.55	1.30, 1.84		3.56	2.48, 5.11		3.74	2.18, 6.41	
	Women vs. MSW	1.01	0.83, 1.22		1.23	0.85, 1.79		0.95	0.60, 1.49	
Calendar year of cART initiation	Per year	0.98	0.96, 1.00	0.030	0.86	0.82, 0.91	<.0001	0.89	0.83, 0.95	0.0005
Individuals not excluded if missing baseline VL and CD4 count (complete case analysis)										
Gender/ sexual orientation	MSW vs. MSM	1.31	1.11, 1.55	0.0002	1.56	1.15, 2.13	<.0001	1.57	1.12, 2.21	0.0052
	Women vs. MSW	1.32	1.14, 1.52		1.91	1.49, 2.45		1.57	1.15, 2.14	
	Women vs. MSW	1.00	0.85, 1.19		1.22	0.91, 1.64		1.00	0.71, 1.40	
Calendar year of cART initiation	Per year	0.92	0.84, 1.00	0.045	0.93	0.90, 0.96	<.0001	0.96	0.92, 0.99	0.021
Virological non-suppression defined using a VL measurement between six and 18 months after cART initiation										
Gender/ sexual orientation	MSW vs. MSM	1.53	1.23, 1.90	<.0001	1.56	1.16, 2.11	0.0001	1.62	1.16, 2.25	0.025
	Women vs. MSW	1.44	1.19, 1.75		1.69	1.32, 2.18		1.28	0.93, 1.76	
	Women vs. MSW	0.94	0.76, 1.17		1.08	0.81, 1.44		0.79	0.56, 1.10	
Calendar year of cART initiation	Per year	0.93	0.91, 0.96	<.0001	0.91	0.88, 0.94	<.0001	0.93	0.90, 0.97	0.0003

[a] Multivariable model included gender/sexual orientation, year of cART initiation, age, baseline VL, baseline CD4 count, initial cART regimen; denominators are provided in Table 6.1; [b] likelihood ratio test; RR= risk ratio; aRR= adjusted risk ratio; NNRTI= Non-Nucleoside Reverse Transcriptase Inhibitors; PI= Protease Inhibitors.

Table 6.19: Associations of the interaction between gender/sexual orientation and calendar year of cART initiation with virological non-suppression 12-18 months after cART initiation – sensitivity analyses

Factors		Strategy A (missing=failure)			Strategy B (missing=excluded)			Strategy C (on cART)		
		aRR [a]	95% CI	P-value[b]	aRR [a]	95% CI	P-value[b]	aRR [a]	95% CI	P-value[b]
Viral load cut-off changed to 200 copies/mL (instead of 50 copies/mL)										
Relative change per calendar year of cART initiation	MSM	1.00	1.02, 1.04	0.053	0.83	0.76, 0.90	0.36	0.87	0.76, 1.00	0.50
	MSW	0.95	0.91, 0.99		0.86	0.77, 0.97		0.85	0.75, 0.96	
	Women	0.96	0.92, 0.99		0.89	0.84, 0.95		0.92	0.84, 1.02	
Individuals not excluded if missing baseline VL and CD4 count (complete case analysis)										
Relative change per calendar year of cART initiation	MSM	1.00	0.98, 1.03	0.047	0.93	0.89, 0.98	0.75	0.98	0.93, 1.04	0.18
	MSW	0.96	0.93, 1.00		0.90	0.84, 0.98		0.90	0.83, 0.97	
	Women	0.96	0.94, 0.99		0.93	0.89, 0.97		0.96	0.90, 1.02	
Virological non-suppression defined using a VL measurement between six and 18 months after cART initiation										
Relative change per calendar year of cART initiation	MSM	0.95	0.91, 0.98	0.23	0.91	0.86, 0.95	0.99	0.94	0.89, 0.99	0.94
	MSW	0.95	0.90, 1.00		0.91	0.85, 0.98		0.93	0.86, 1.00	
	Women	0.91	0.87, 0.94		0.91	0.86, 0.95		0.92	0.86, 0.99	

[a] Adjusted for age, baseline VL and CD4 count, initial ART regimen; [b] likelihood ratio test; aRR= adjusted risk ratio.

6.5 **Discussion**

6.5.1 **Summary of results**

- Overall, among people starting cART in the UK, the risk of virological non-suppression at one year is now low. The results of this chapter have demonstrated that the risk of virological non-suppression at 12 or 24 months after starting cART has decreased over calendar year of cART initiation for all gender/sexual orientation groups.
- However, even in the most recent years, women and MSW remained at a greater risk of virological non-suppression than MSM.
- Overall there was no evidence that differences in the risk of having a VL >50 copies/mL at 12 or 24 months after cART initiation between the gender/sexual orientation groups were narrowing.
- The interaction term between gender/sexual orientation and calendar time was only found to be associated with virological non-suppression at 12 months when I considered those LTFU as having virological non-suppression (analysis strategy A), and not under the other two analysis strategies. Thus, the greater improvements over time in virological response among MSW and women (compared to MSM) reflected the lower percentage of individuals in these groups who were LTFU in more recent compared to earlier years. Furthermore, when those who initiated ART between 2012 and 2014 were removed there was no evidence that the interaction term was associated with virological non-suppression.
- For every calendar year of cART initiation later, the risk of interrupting treatment within 12 months of cART initiation decreased by 9% and the risk of <80% cART adherence decreased by 5% on average.
- Women and MSW had a greater risk of both cART non-adherence and interruptions compared to MSM. Notably, women were at over twice the risk of cART interruption in the first 12 months compared to MSM, which puts them at a disadvantage for achieving virological suppression – a disadvantage that does not seem to have diminished over time.
- The results of this chapter suggest that cART non-adherence and interruptions explain at least part of the differences in virological non-suppression at 12 months by gender/sexual orientation.

6.5.2 **Interpretation of results**

The reductions in risk over calendar year of cART initiation were more substantial when individuals with a missing VL were excluded (strategy B) than when restricted to individuals on cART at the time of their VL measurement (strategy C). When I investigated whether cART disruptions were a mediator for the association between gender/sexual orientation and virological non-suppression, there was evidence that treatment disruptions somewhat attenuated this association, and the association between increasing calendar year of cART initiation and decreasing risk of virological non-suppression. It is likely, therefore, that the greater improvements over time seen in analysis strategy B compared to strategy C arose in part from reductions in cART interruptions for people starting cART in later calendar years.

Adjustment for cART interruptions attenuated the differences in virological non-suppression between MSW and MSM and between women and MSM to a greater extent than adjustment for cART prescription coverage, as a measure of adherence. This may have reflected the greater accuracy of the measurement of cART interruptions compared to adherence (see Section 6.5.3). However, it is also likely that, since cART interruptions are a more extreme form of non-adherence these behaviours are more able to account for poorer virological outcomes. On the other hand, the difference in the extent to which these factors explained the differences in virological non-suppression could also be a result of the measure of non-adherence failing to capture true adherence levels (see Section 6.5.3).

The reductions in cART interruptions over time were likely in part related to the introduction of one tablet once a day regimens[604], less toxic ARVs[605] and better clinical management with regard to adherence. However, since there were not substantial differences in the cART regimens used by gender/sexual orientation in this chapter, these factors were unlikely to explain the greater prevalence of treatment interruptions found among women compared to MSM and MSW. Differences with by gender/sexual orientation respect to socio-economic status (SES), time in the UK, family circumstances, pregnancy, psychosocial factors and comorbidities may be related to gender/sexual orientation disparities in ART adherence and in turn virological outcomes. As shown in Section 2.5, several studies have found that lower SES is associated with poorer virological response[126;342;359;363;400-405;408;415], but further study of the role of these factors in a UK setting is required. It was not possible to assess the impact of these factors in this chapter since they are unavailable in the Royal Free cohort study, as is the case with many cohorts that use routinely collected data; however, I look at SES and social circumstances in Chapters 7 and 8.

Other than gender/sexual orientation and calendar year of cART initiation, age at cART initiation and initial cART regimen were found to affect initial virological response. Younger age was associated with a greater prevalence of virological non-suppression at 12 and 24 months after cART initiation, similarly to other recent cohort studies[596;606;607]. Adjustment for cART disruptions within 12 months of cART initiation attenuated the association between younger age and poorer virological response at 12 months to some extent. A greater prevalence of treatment disruptions among younger individuals were also found in several other studies[588;608;609]. NNRTI-based initial cART regimens were also associated with a lower prevalence of virological non-suppression at 12 months compared to PI-based or other regimens under analysis strategies B and C. There was no evidence of an association between initial cART regimen and virological response at 24 months after cART initiation though, so it is likely that any effect of initial treatment is short-term. However, choice of initial regimen does have an effect in the long-term on what subsequent regimens may follow if drug-resistance develops[610]. Unlike gender/sexual orientation and age differences, the association between initial cART regimen and virological non-suppression was not substantially attenuated by adjustment for cART disruptions. Thus, its effect on initial virological response is likely through time until an initial period of viremia[611].

6.5.3 **Strengths and Limitations**

The variety of outcome measures under consideration are a major advantage to this chapter, in that it tests the robustness of any differences or associations found. Three analysis strategies were considered for the virological outcomes, including the use of a missing=failure analysis, in order to give a more complete picture of the trends. Additionally I considered two definitions of cART disruptions/interruptions and two more of cART adherence. Treatment disruption data came from patient notes recorded by HIV clinicians, which were 100% notes, reviewed annually, with attempts made to record treatment disruptions as short as two to three days; therefore, the data on ARVs stopped or switched for others should be highly accurate. However, it is possible that some treatment disruptions could have been missed, since the collection of this data requires the individual to report that they stopped taking their treatment. Thus treatment disruptions in this chapter may have been underestimated.

An advantage of the data being from a single centre is that the patients should have received fairly homogenous care, e.g. similar resources available (and this would be difficult to capture in routinely collected data), and the data collection was homogenous. Furthermore, in a multicentre study, if there were differences in the

proportion of MSM at the different clinics, then it may be difficult to distinguish the role of gender/sexual orientation. A single centre study avoids this problem.

One important limitation of this chapter was the amount of baseline missing VL data, which meant that it was not possible to include the whole population starting cART. However, I considered a sensitivity analysis addressing this issue, which gave similar results. Furthermore, 18% (356) of those included in strategy A were excluded under strategy B no VL measurement in the six-month window, 12-18 months after baseline. In a sensitivity analysis where the window was widened to between six and 18 months after cART initiation, only 8% (167) were excluded because they did not have a VL measurement within the period. There was also a large proportion of individuals without prescription-based adherence data who were excluded for the analyses including the cART non-adherence measure. However, there was not another measure of adherence available from the RFHCS and restrictions for a prescription-based measure must be such that individuals can be reasonably assessed to be collecting prescriptions from the pharmacy.

Prescription refill was the only measure currently available for measuring adherence in this cohort, and this measure was only available for about half of the patients for which it was relevant. The advantage of measuring adherence by using prescription refill data is that it does not suffer from the social desirability or self-reporting bias. Additionally, these data can be collected easily and cheaply in most healthcare settings. One disadvantage of prescription based adherence measures is that they can only be used in a closed pharmacy system. It is possible that individuals could have accessed treatment from another source, however, this was considered as unlikely to any large degree due to the inclusion criteria, since the HIV pharmacy is co-located at the HIV clinic, and the fact that only specialist pharmacies can dispense ARVs. Another drawback of the measure is that it considered individuals to be adherent on the basis that they had been prescribed enough treatment to enable complete adherence, but this does not mean that the treatment had actually been taken. Likewise, the measure that was used only recorded the issue of prescriptions and not whether those prescriptions had actually been collected. Prescription based measures cannot fully capture the number of doses missed; however, studies have found good agreement between these measures of adherence and electronic adherence monitors[612].

The method of adjusting for non-adherence or disruptions in order to assess whether they mediate the association between gender/sexual orientation and virological non-suppression works through blocking the causal pathway, however, as a result it may

lead to intermediate confounding[613]. Furthermore, the effect of non-adherence or cART disruptions in attenuating gender/sexual orientation associations with virological non-suppression would be underestimated when assessed by change in magnitude of estimates that were already adjusted for baseline factors, as the effect of adherence may have been partially captured by this initial adjustment. Adjustment for cART non-adherence may not be expected to fully attenuate the association between gender/sexual orientation and virological non-suppression due to inadequacy of the prescription based measure as an accurate measure of non-adherence over the whole time-period. Furthermore, the overall measure would not necessarily capture non-adherence at the most critical time in relation to the VL measurement on which the outcome was based.

Other limitations of this chapter concern the measurement of the virological outcomes. Virological non-suppression may be underestimated because of its definition using a single VL measurement >50 copies/mL closest to 12 months after ART initiation, which could miss any VL >50 copies/mL before and after this measurement. However, such a strategy based on VL at a fixed time point is likely to be preferable to a 'time to event' type analysis which would be more likely to capture transient viremia and may also be more influenced by frequency of VL measurement. A recent study in the Australian HIV Cohort found that even a single VL between 50 and 199 copies/mL was predictive of over four times higher risk of subsequent virological failure (VL >200 copies/mL)[555]. Furthermore, the results were consistent in the sensitivity analysis where virological non-suppression was defined by a VL >200 copies/mL. Since strategy A is a missing=failure analysis, the outcome of virological non-suppression at 24 months is dominated by the number of individuals without a measurement in the six-month window considered. Even among individuals LTFU from the Royal Free HIV cohort, this does not mean that they are necessarily not engaged in care anymore. In fact, as people with HIV are free to transfer their care between the many HIV treatment centres in London as they wish, transfer of patients between centres is likely to be very common. Thus, assuming that all individuals without a VL measurement are virologically non-suppressed is likely to be an over-estimate. Therefore, it could be concluded that the 'true' proportion with virological non-suppression one year after starting cART is likely to lie between results for strategy A and strategy B.

This analysis considered initial response to first cART. Therefore, the associations and trends over time found may not be generalisable to longer-term response or to second or third-line regimens. Moreover, data came solely from a single centre in a UK setting, and therefore the results may not be able to be extrapolated to the UK or to other

geographic settings with different healthcare systems. However, the characteristics of individuals attending the Royal Free HIV outpatient clinic are generally similar to the HIV positive population in the UK (discussed further in Section 10.2).

In terms of the measure of reasons for cART disruptions, the reasons recorded were clinician-completed, so it is possible that they were not representative of the actual reasons that individuals had disrupted treatment[614]. Furthermore, categories such as toxicities as reasons for disrupting treatment does not necessarily capture the reason why an individual was having difficulties in coping with toxicities. Reasons such as "patient choice", "poor compliance", or "other" give even less insight into the cause of treatment disruption. A qualitative questionnaire study would likely be more able to collect this information.

6.6 **Conclusions**

Over the study period, virological response to first-line cART at 12 and 24 months substantially improved among all three gender/sexual orientation groups and the prevalence of treatment non-response to first-line cART in recent years has been low. However, this chapter highlighted that even in a high-income setting with universal free access to healthcare, such as the UK, MSW and women are at higher risk of an initial virological non-response. These differences, albeit relatively small in absolute terms, persisted in the most recent years, and there was no evidence that differences were narrowing over time. Emphasis should be placed on tailoring support for MSW and women with HIV.

Chapter 7 Socio-economic factors and cross-sectional and longitudinal virological outcomes for HIV-positive people on ART in the UK: results from the ASTRA study

7.1 Objectives

- To investigate the association of socio-economic factors with ART non-adherence and virological non-suppression in cross-sectional analyses, and virological rebound in longitudinal analyses, among HIV-positive people on ART in the ASTRA study, a multi-centre UK-based study.
- To investigate the extent to which any socio-economic associations with virological outcomes were mediated by a self-reported measure of ART non-adherence.

7.2 Introduction

There is substantial evidence of socio-economic inequalities in the prognosis of a number of diseases, including cancer, diabetes, and cardiovascular disease[305;315-318;437-440;615;616]. Further studies have found evidence that lower socio-economic status (SES), measured by education or income, is associated with poorer adherence to treatment, such as steroids for asthma[617], insulin for diabetes[618] and anti-depressants[619].

HIV-positive populations in high-income settings comprise distinct demographic groups, with substantial variation in social circumstances[620] and a high proportion of migrants[269;327]. As such, social inequalities may also impact on disparities in HIV health outcomes[621]. Although the literature review in Section 2.5 identified some evidence of an association between socio-economic deprivation and poorer ART response in US studies[402;403;409;622], few studies had addressed this question in settings with universal access to healthcare. Two European studies found that lower level of education[126;405] was associated with poorer virological outcomes of ART, and a further study found an association between unemployment[342] and poorer virological response to ART. It is likely that neither education nor employment status alone are able to adequately capture current socio-economic hardship. One further cross-sectional study in France used several markers of socio-economic disadvantage: lower education level, unemployment and material deprivation and found each to be inversely associated with sustained virological suppression (unadjusted odds ratio [OR]=0.5-0.6)[359]. There

have been no previous studies of socio-economic variations in virological outcomes in the UK.

Socio-economic factors might have less impact on HIV prognosis in settings with universal access to HIV diagnosis and treatment, since this should considerably lessen financial barriers to accessing ART. Thus, one may expect that findings from countries such as the US may not be replicated in these settings. If socio-economic deprivation were associated with poorer treatment response in settings such as the UK, then this would imply that the effects of SES go beyond ability to pay for healthcare. Therefore, study of the association between lower SES and ART outcomes in these settings may help to shed light on the mechanisms by which it operates.

As discussed in Section 2.6.2.1 , non-adherence to ART is the fundamental driver of virological response[170;455]. The correlation between measures of non-adherence and failure to achieve virological suppression is well documented[455;623;624]. Moreover, there is evidence that poorer SES (measured by education, employment, and social support) is associated with ART non-adherence from some European studies[346;625-627]. Thus, any impact of SES on virological outcome is likely to be mediated in part through differential patterns of adherence to ART.

7.3 **Methods**

7.3.1 **Study design**

The Antiretrovirals, Sexual Transmission Risk and Attitudes (ASTRA) study is a cross-sectional, questionnaire study of 3258 HIV-diagnosed individuals recruited from eight HIV outpatient clinics in the UK in 2011/2012 (64% response rate), which was described in detail in Section 4.3 and in a paper by Speakman et al.[516]. Participants self-completed a confidential questionnaire on socio-demographic, health and lifestyle issues. Study personnel recorded the most recent VL and CD4 count results available at the time of the questionnaire for all participants. Six of the eight study centres provided linkage to routine HIV clinical records (including serial VL measurements) for consenting participants (2983 [92%]) using a pseudo-anonymised study number. Thus, cross-sectional analyses were performed in order to assess associations between both non-adherence and with virological non-suppression at the time of the questionnaire with SES. Additionally, longitudinal analyses were performed to assess the association of subsequent virological rebound with SES, among people with virological suppression at the time of the questionnaire.

7.3.2 Outcomes of interest

7.3.2.1 *ART non-adherence*

ART non-adherence was considered as a binary variable. A broad definition was used in order to capture any potential non-adherence. Thus, non-adherence was defined as either an affirmative response to the question: “In the past three months, have you ever missed your HIV treatment for two or more days at a time?” or reporting one or more missed doses in response to the question: “In the last two weeks, how many doses of HIV treatment have you missed?”

7.3.2.2 *Virological non-suppression*

Virological non-suppression was defined as a single VL >50 copies/mL at the time of the questionnaire. The VL was reported by the clinic (i.e. patient-reported VLs were not considered). This VL was either that recorded by the study team at the time of questionnaire completion, or that obtained from the linked clinical data provided by the participating site, depending on which was the latest VL value at the time of the questionnaire.

7.3.2.3 *Virological rebound*

Individuals were followed from baseline until virological rebound (defined as the first VL >200 copies/mL) or the last available VL (latest October 2015). Since continuous ART is recommended, follow-up was not censored at ART interruption[162].

7.3.3 Inclusion criteria

7.3.3.1 *ART non-adherence*

All ASTRA study participants who met the following criteria were considered for inclusion: (i) on ART at the time of the questionnaire, (ii) a non-missing value for age, and (iii) a non-missing value for at least one of two ART-adherence questions. On ART was defined by an affirmative response to the question from the questionnaire: “Are you currently taking HIV treatment?” Thus unlike Chapters 5 and 6, individuals on a regimen of fewer than three ARVs were included. However, as the ASTRA study was conducted between 2011 and 2012, most individuals were likely on cART regimens.

7.3.3.2 *Virological non-suppression*

Analyses considering virological suppression additionally required: (i) a non-missing value for VL; (ii) a non-missing value for the date of ART initiation; (iii) started ART at least six months prior to the VL measurement being used for analysis (for the reasons described in Section 5.3.3[367;556-560]). Thus, these analyses took a missing=excluded approach.

7.3.3.3 *Virological rebound*

Consenting ASTRA participants from the six centres for which linked longitudinal clinic data were available were considered. Baseline was defined as the date of questionnaire issue. Inclusion criteria were: (i) on ART with a VL ≤50 copies/mL at baseline (latest value at the time of the questionnaire); (ii) non-missing value for age at baseline; (iii) non-missing value for at least one ART-adherence question; (iv) started ART at least six months prior to the date of the "baseline VL measurement" (so that individuals had had a chance to have reached virological suppression); (v) at least one VL measurement subsequent to baseline.

7.3.4 **Covariates of interest**

Four questions in the ASTRA study, discussed in Section 4.4.2.3 , were directly related to SES and thus form the primary covariates of interest in my analysis:

- Ability to afford basic needs (financial hardship with four levels)
- Employed (yes; no)
- Housing status (homeowner; renting; unstable/other)
- University education (yes; no).

In addition, I considered five questions related to social circumstance in order to provide supportive evidence on the association between SES and virological outcomes to ART:

- Time living in the UK (UK-born; >5 years; ≤5 years)
- English reading ability (UK-born; fluent; not fluent)
- Supportive network (most; medium; least)
- Children (yes; no)
- Current partner (yes; no).

The demographic factors considered in this analysis were gender/sexual orientation (MSM; MSW; women), ethnicity (white; black African; other), and age (as a continuous variable). The gender/sexual orientation variable was based on self-reported sexual orientation, rather than the likely mode of HIV transmission, as it was in the previous two chapters. Therefore, individuals who acquired HIV through routes other than sexual intercourse were included in this chapter. Demographic factors were not the focus in this chapter but were explored in detail in Chapter 8.

Information on how each of the variables were derived from the original ASTRA study questions is given in Section 4.4.2.

7.3.5 **Statistical analysis**

7.3.5.1 ***Cross-sectional analyses***

The prevalences of ART non-adherence and virological non-suppression were summarised according to the demographic, socio-economic, and social circumstance factors. The groups were compared using Chi-squared tests or Cochran-Armitage tests for trend for ordered categorical variables. Spearman correlation coefficients were calculated to measure the correlations between all of the covariates. This was used to check for collinearity, so that highly correlated variables were not included in the same model. Correlation tables are useful in understanding associations and providing supplementary information to assess the extent to which model choices are supported, but they were not the basis by which I decided what covariates to include.

In order to investigate the association of socio-economic and social circumstance factors with ART non-adherence and virological non-suppression, unadjusted prevalence ratios (PRs) and adjusted prevalence ratios (aPRs) were generated using modified Poisson regression models[526]. Each socio-economic/social circumstance factor was considered in a separate model to avoid the negative effects of collinearity. Furthermore, this made it possible to evaluate how each different marker of SES may relate to ART response individually, rather than in addition to that explained by the other SES markers. As in previous chapters, multivariable models were adjusted for gender/sexual orientation and age, but not ethnicity. This was in part due to its high collinearity with gender/sexual orientation (see Section 4.4.1), but also because it was thought likely that any effect of ethnicity on ART outcomes would largely reflect the effect of social factors. Therefore, ethnicity would be acting as a marker of SES, and its inclusion as an independent variable would potentially weaken an association between a specific SES factor and virological outcome.

The association between ART non-adherence and virological non-suppression was also assessed using modified Poisson regression, where ART non-adherence was considered as a covariate rather than an outcome. ART non-adherence was then added to each multivariable regression model in turn to investigate the extent to which the associations between SES markers and virological non-suppression were attenuated by this potential mediating factor (see Section 6.3.5 for the assumptions underlying this).

7.3.5.2 ***Longitudinal analyses***

In order to check the validity of using time-to-event analyses, I considered the median number of VL measurements by each SES and social circumstance factor. The association of socio-economic/social circumstance factors with time to virological

rebound were assessed using Kaplan-Meier plots and Cox proportional hazards regression models, where each factor was considered in a separate model; firstly unadjusted and then adjusted for demographic factors (gender/sexual orientation and age). Additionally, the association between ART non-adherence and virological rebound was assessed using Cox proportional hazards regression.

7.3.5.3 *Analyses of the subgroups white MSM and black African heterosexuals*

All cross-sectional and longitudinal analyses were repeated, where the study population was restricted to the subgroups of: (i) MSM of white ethnicity; and (ii) MSW and women of black African ethnicity. The rationale for these subgroup analyses was to reduce confounding by race, gender, and sexual orientation.

7.3.5.4 *ART non-adherence as a mediator of the association between SES and virological response to ART*

Additional analyses assessed the extent to which the association between socio-economic/social circumstance factors and virological response changed when ART non-adherence was also included as a covariate. Modified Poisson regression was used to assess whether ART non-adherence was a mediator of the association between SES and virological non-suppression. Cox proportional hazards regression was used to assess whether ART non-adherence attenuated associations between SES and virological rebound.

7.3.6 **Sensitivity analyses**

Firstly, for the analysis with ART non-adherence as an outcome, a sensitivity analysis was conducted where individuals who had been on ART previously but were not on ART at the time of the questionnaire, were defined as non-adherent. Secondly, a cross-sectional sensitivity analysis for the virological suppression outcome was performed, considering a VL cut-off of 200 copies/mL instead of 50 copies/mL. Finally, two longitudinal sensitivity analyses were performed for the virological rebound outcome where: (i) the outcome was defined as two consecutive VL measurements >200 copies/mL to investigate an endpoint of sustained virological rebound[628]; and (ii) those who were lost to follow-up (LTFU) were considered as having experienced virological rebound six months after the date of the last available VL measurement, as lack of retention in HIV care has been found to be associated with poorer prognosis[629]. In the last analysis described, LTFU was defined as eligible for the analysis but date of last measurement was >18 months prior to administrative censoring date.

7.3.7 **Missing data**

Complete-case analyses were performed throughout, as the proportion of participants with missing data did not exceed four percent for any variable used in the analysis.

Twelve percent of participants had missing data for at least one variable. However, only individuals with missing data for any of the demographic, SES, or social circumstances covariates included in a particular model were excluded from that model. Thus, the percentage of individuals excluded due to missing data in any model was always below 12%.

7.4 **Results**

7.4.1 **Participant characteristics**

Of 3258 individuals (69% MSM, 11% MSW, 20% women) who participated in the ASTRA study, 2771 (85%) reported being on ART at the time of the questionnaire. The remaining 487 (15%) not on ART included: 366 (11%) ART naïve individuals; 65 (2%) individuals who had stopped ART; 56 (2%) with missing ART information. Of the 2771 participants currently on ART, 58 (2%) had missing age, and nine (<1%) had not responded to either adherence question, thus were excluded. This resulted in 2704 individuals being included (1867 MSM, 321 MSW, 516 women), whose characteristics are shown in Table 7.1. The majority (80%) had been diagnosed with HIV for over five years. Participants reported having been on ART for a median of 6.9 years (interquartile range [IQR] = 2.8-12.4 years). Median clinic-recorded CD4 count was 546 cells/μL (IQR = 393-732 cells/μL) and 2276 (87%) individuals had a VL ≤50 copies/mL at the time of the questionnaire. Overall, 55% of participants were employed, 35% were homeowners, and 40% were university educated. Of note, over half of participants reported that they did not always have enough money to cover their basic needs.

Table 7.1: Characteristics of questionnaire respondents included in cross-sectional and longitudinal analyses

Factor		Cross-sectional: ART non-adherence analysis [a]		Cross-sectional: virological non-suppression analysis [b]		Longitudinal: virological rebound analysis [c]	
		N	%[d]	N	%[d]	N	%[d]
Total		2704	100	2405	100	1740	100
Gender/sexual orientation	MSM	1867	69	1670	69	1267	73
	MSW	321	12	277	12	171	10
	Women	516	19	458	19	302	17
Mode of HIV acquisition	Sex between men	1748	65	1571	65	1195	69
	Heterosexual sex	536	20	472	20	314	18
	PWID	46	2	42	2	25	1
	Other	353	13	303	13	197	11
	Missing	21	1	17	1	9	1
Ethnicity	White	1875	69	1670	69	1259	72
	Black African	507	19	460	19	281	16
	Black Other	89	3	78	3	52	3
	Other	184	7	153	6	113	6
	Missing	49	2	44	2	35	2
Age	Median (IQR)	46 (40, 52)		46 (40, 52)		46 (41, 52)	
Afford basic needs (financial hardship)	Always	1170	43	1038	43	814	47
	Mostly	701	26	627	26	454	26
	Sometimes	464	17	412	17	265	15
	No	326	12	290	12	176	10
	Missing	43	2	38	2	31	2
Employment	Employed	1479	55	1302	54	985	57
	Unemployed	483	18	425	18	286	16
	Sick/ disabled	375	14	344	14	224	13
	Retired	180	7	165	7	129	7
	Other	127	5	115	5	79	5
	Missing	49	2	54	2	37	2
Housing	Homeowner	914	35	852	35	658	38
	Renting from council	840	31	763	32	522	30
	Renting privately	609	23	523	22	393	23
	Temporary/homeless	70	3	58	2	35	2
	Staying with family	191	7	162	7	97	6
	Other	10	<1	10	<1	6	<1
	Missing	40	1	37	2	29	2
Education (highest level)	≥University degree	1094	40	977	41	759	44
	A-level or equivalent	536	20	484	20	338	19
	O-levels or equivalent	601	22	529	22	364	21
	Other	108	4	97	4	70	4
	None	302	11	260	11	169	10
	Missing	63	2	58	2	40	2
Time in UK	Born in UK	1511	56	1329	55	983	56
	> 5 years	991	37	899	37	635	36
	≤ 5 years	116	4	98	4	68	4
	Missing	86	3	79	3	54	3
English reading ability	Born in UK	1511	56	1329	55	983	56
	Fluent	912	34	825	34	595	34
	Not fluent	208	8	182	8	114	7
	Missing	73	3	69	3	48	3
Supportive network	Most support	878	32	762	32	562	32
	Medium support	1414	52	1273	53	930	53
	Least support	377	14	342	14	227	13

Factor		Cross-sectional: ART non-adherence analysis [a]		Cross-sectional: virological non-suppression analysis [b]		Longitudinal: virological rebound analysis [c]	
		N	%[d]	N	%[d]	N	%[d]
	Missing	35	1	28	1	21	1
Children	Yes	733	27	661	27	426	24
	No	1954	72	1729	72	1305	75
	Missing	17	1	15	1	9	1
Partner	Yes	1530	57	1363	57	997	57
	No	1158	43	1026	43	731	42
	Missing	16	1	16	1	12	1
Time since HIV diagnosis	< 2 years	180	7	107	4	64	4
	2 – 5 years	361	13	304	13	222	13
	5 – 15 years	1345	50	1266	53	926	53
	> 15 years	755	28	723	30	528	30
	Missing	63	2	5	<1	0	0
Number of times taking ART per day	1	2159	80	1902	79	1419	81
	≥2	513	19	476	20	309	18
	Missing	32	1	27	1	21	1
Self-reported ≥2 consecutive missed days of ART in past 3 months	No/ don't know	2236	83	1973	82	1461	84
	Yes	464	17	429	18	277	16
	Missing	4	<1	3	<1	2	<1
Self-reported ≥1 missed dose in the last 2 weeks	No/ don't know	2022	75	1777	74	1289	74
	Yes	676	25	624	26	447	26
	Missing	6	<1	4	<1	4	<1
ART Non-adherent [e]	No/ don't know	1831	68	1601	67	1174	67
	Yes	873	32	804	33	566	33
Time on ART (years) [f]	Median (IQR)	6.9 (2.8, 12.4)		7.7 (3.7, 12.9)		7.7 (3.7, 12.9)	
CD4 count (cells/μL) [g]	Median (IQR)	546 (393, 732)		560 (410, 749)		590 (442, 780)	
VL at time of the questionnaire	≤50 copies/mL	2276	87	2186	91	1740	100
	>50 copies/mL	329	13	219	9	0	0
	Missing	16	1	0	0	0	0

[a] All participants who self-reported being on ART at the time of the questionnaire and had recorded age and non-adherence information; [b] all participants who self-reported being on ART at the time of the questionnaire, had recorded age and non-adherence information, recorded VL and date of ART initiation, and started ART >6 months prior to completion of the questionnaire; [c] all participants had linked clinical data, recorded age and non-adherence information, were on ART, had VL ≤50 copies/mL at the time of the questionnaire, started ART >6 months before the baseline VL measurement, and had ≥1 subsequent VL measurement; [d] some column percentages do not sum to 100% due to rounding; [e] self-reported ART non-adherence: ≥2 consecutive missed days of ART in the past 3 months or ≥1 missed dose in the last 2 weeks; [f] missing time on ART: cross-sectional (ART non-adherence) N=99, cross-sectional (virological non-suppression) N=0, and longitudinal N=0; [g] missing CD4 count: cross-sectional (ART non-adherence) N=17, cross-sectional (virological non-suppression) N=5, and longitudinal=2; PWID=people who inject drugs; IQR=interquartile range.

Figure 7.1 displays spearman's rank correlation coefficients for the bivariate correlations between each of the covariates. There was a moderate correlation observed between gender and sexual orientation, which lent support to the decision to include these as a combined variable in the analyses. The associations observed between ethnicity and both time in the UK and English reading ability was one rationale in the decision not to adjust the models for ethnicity, since it was at least partially acting as a marker of social circumstances. Having children, gender, sexual orientation and ethnicity all had a moderate correlation with one another.

Figure 7.1: Spearman Correlation Coefficients between demographic, socio-economic and social circumstances factors[630]

	Financial hardship	Employment	Housing	Education	Time in UK	Reading ability	Social support	Children	Partner	Gender	Sexual orientation	Ethnicity	Age
Financial hardship	1.00	0.39	0.41	0.23	0.20	0.24	0.26	0.25	-0.11	0.25	0.29	0.32	-0.07
Employment		1.00	0.23	0.19	0.01	0.04	0.23	0.12	-0.15	0.08	0.11	0.10	0.18
Housing			1.00	0.20	0.27	0.28	0.12	0.17	-0.12	0.21	0.26	0.30	-0.22
Education				1.00	-0.07	-0.03	0.05	0.10	-0.08	0.07	0.07	0.03	0.02
Time in UK					1.00	0.97[a]	0.00	0.29	-0.00	0.35	0.43	0.56	-0.14
Reading ability						1.00	0.01	0.33	-0.01	0.37	0.45	0.58	-0.13
Social support							1.00	-0.02	-0.31	0.02	-0.01	0.00	0.04
Children								1.00	0.03	0.51	0.66	0.50	0.06
Partner									1.00	-0.03	0.05	0.02	-0.04
Gender										1.00	0.69	0.52	-0.13
Sexual orientation											1.00	0.64	-0.08
Ethnicity												1.00	-0.15
Age													1.00

Key [b]		
	0.9 to 1.0	Very high correlation
	0.7 to 0.9	High correlation
	0.5 to 0.7	Moderate correlation
	0.3 to 0.5	Low correlation
	< 0.3	Negligible correlation

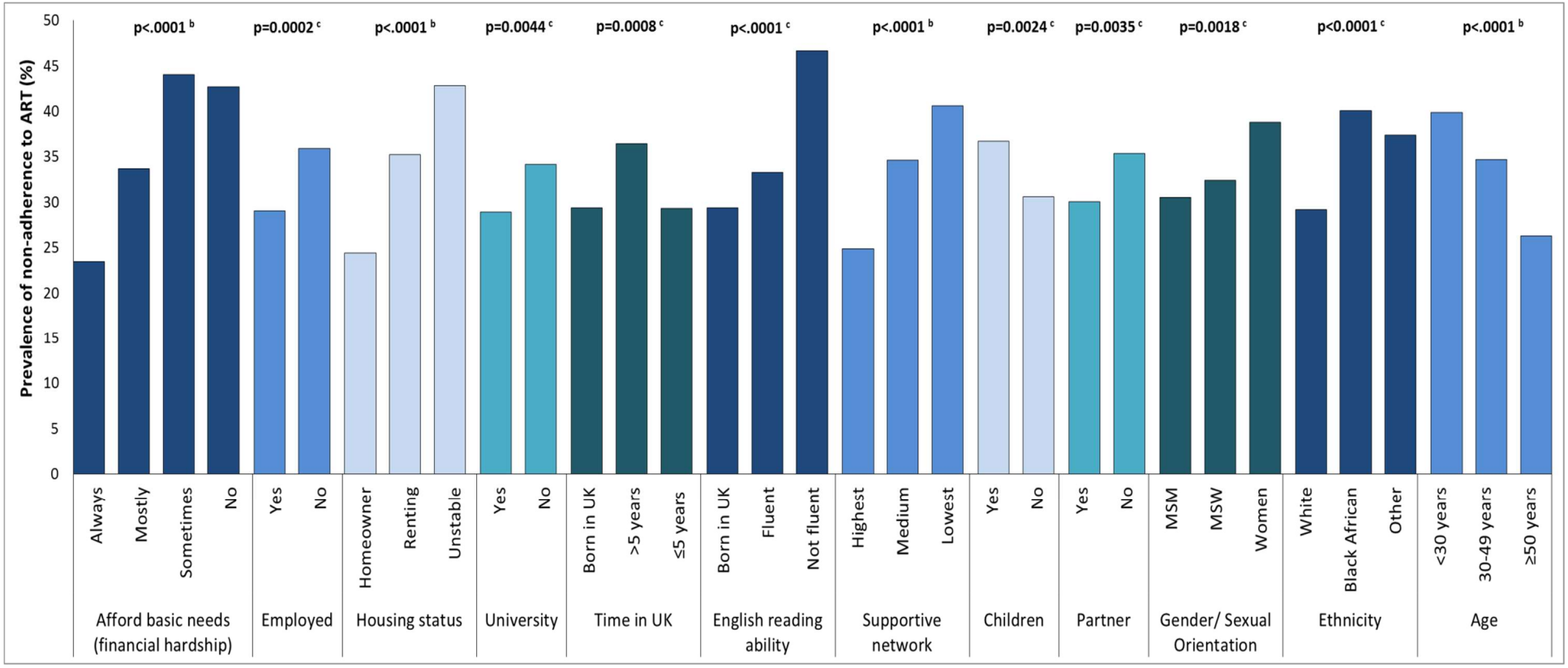
[a] Time in the UK and English reading ability had one identical group for individuals born in the UK so inevitably have a very strong correlation; [b] this key denotes absolute values.

7.4.2 **SES and ART non-adherence**

Of the 2704 participants on ART, 873 (32%; 95% CI: 31%, 34%) reported ART non-adherence. Individuals with poorer SES by any measure – increased financial hardship, non-employment, rented or unstable housing status, and non-university education – were more likely to have reported ART non-adherence (Figure 7.2). In terms of social circumstance factors, reporting ART non-adherence was associated with living in the UK for over five years but not being born in the UK (with lower levels of non-adherence among the two other groups); non-fluent English reading ability; lowest supportive network; having children; and not having a current partner. Women were most likely to report ART non-adherence, followed by MSW and then MSM. Black African and other ethnicity and lower age were also associated with reporting ART non-adherence compared to white ethnicity and older age respectively.

Unadjusted associations of socio-economic factors and social circumstances with ART non-adherence are shown in terms of PRs in Table 7.2. After adjustment for demographic factors (gender/sexual orientation and age), all measures of poorer SES remained associated with a greater prevalence of ART non-adherence. These were attenuated by 1-14%, with the greatest attenuations for housing status. Likewise, associations of non-adherence with all social circumstance variables remained after adjustment for demographic factors. The association between being fluent or non-fluent in English and greater prevalence of non-adherence compared to UK-born individuals was attenuated by 6% and 10%, respectively. However, adjustment for demographic factors actually increased the PR for the association between living in the UK for fewer than five years and non-adherence; this is likely a result of the correlation between time in the UK and sexual orientation (Figure 7.1).

Figure 7.2: Prevalence of ART non-adherence by socio-economic and demographic factors [a]



[a] Cross-sectional analysis among 2704 respondents who self-reported being on ART at the time of the questionnaire, self-reported ART non-adherence: ≥2 consecutive missed days of ART in the past 3 months or ≥1 missed dose in the last 2 weeks; [b] Cochran-Armitage test for trend; [c] Chi square test.

Table 7.2: Cross-sectional associations of socio-economic factors and social circumstances with ART non-adherence [a] (N=2704)

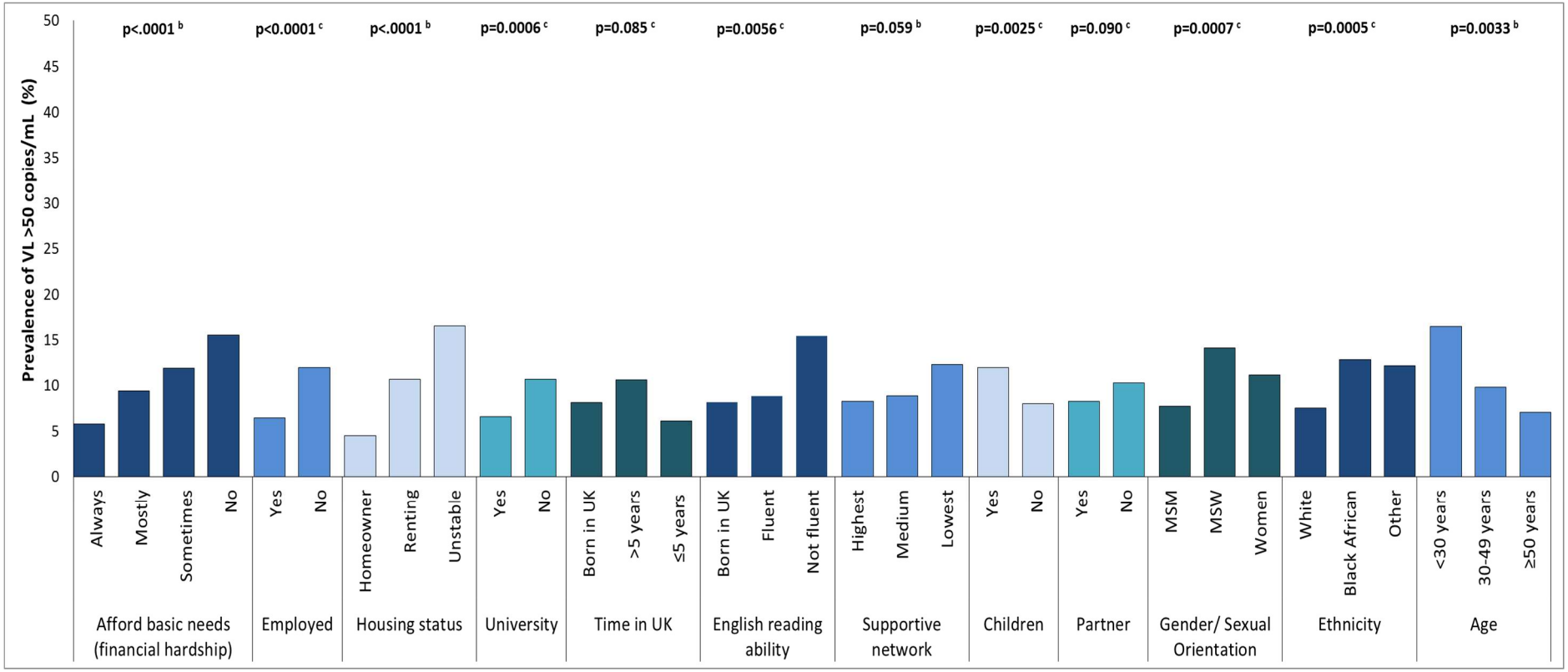
Factors [b]			Unadjusted			Adjusted for gender/sexual orientation and age		
		N	PR	95% CI	P-value[c]	aPR	95% CI	P-value[c]
Enough money for basic needs? (Financial hardship)	Always	1170	1		<.0001 [d]	1		<.0001 [d]
	Mostly	701	1.44	1.24, 1.66		1.43	1.23, 1.65	
	Sometimes	464	1.88	1.62, 2.17		1.85	1.59, 2.15	
	No	326	1.82	1.55, 2.14		1.78	1.50, 2.11	
Employed	Yes	1479	1		0.0002	1		<.0001
	No	1165	1.24	1.11, 1.38		1.29	1.16, 1.45	
Housing status	Homeowner	944	1		<.0001 [d]	1		<.0001 [d]
	Renting	1449	1.44	1.27, 1.65		1.36	1.19, 1.56	
	Unstable	271	1.76	1.47, 2.10		1.62	1.35, 1.95	
University	Yes	1094	1		0.0041	1		0.0050
	No	1547	1.18	1.05, 1.33		1.18	1.05, 1.32	
Time in UK	Born in UK	1511	1		0.0010	1		0.018
	>5 years	991	1.24	1.11, 1.39		1.16	1.02, 1.32	
	≤5 years	116	1.00	0.75, 1.34		0.86	0.63, 1.16	
English reading ability	Born in UK	1511	1		<.0001	1		0.0007
	Fluent	912	1.13	1.00, 1.28		1.07	0.94, 1.22	
	Not fluent	208	1.59	1.35, 1.88		1.49	1.24, 1.79	
Supportive network	Most	878	1		<.0001 [d]	1		<.0001 [d]
	Medium	1414	1.39	1.22, 1.60		1.40	1.22, 1.60	
	Least	377	1.63	1.38, 1.93		1.65	1.39, 1.95	
Children	Yes	733	1		0.0030	1		0.022
	No	1954	0.83	0.74, 0.94		0.83	0.70, 0.97	
Partner	Yes	1530	1		0.0037	1		0.0014
	No	1158	1.18	1.06, 1.31		1.20	1.07, 1.34	

[a] Self-reported ART non-adherence: ≥2 consecutive missed days of ART in the past 3 months or ≥1 missed dose in the last 2 weeks; [b] each socio-economic factor considered in a separate model for all results but gender/sexual orientation and age are included in every model, individuals with missing values for explanatory variables were excluded; [c] Chi square test; [d] test for trend. PR=Prevalence Ratio; aPR=adjusted Prevalence Ratio.

7.4.3 **SES and virological non-suppression**

Of the 2704 participants included in the ART non-adherence analysis, 2605 had a recorded VL at the time of the questionnaire and date of first ART initiation, of whom 2405 had started ART more than six months before the VL measurement. Therefore, the virological non-suppression analysis included 2405 (89%) participants. Of these, 219 (9%; 95% CI: 8%, 10%) had virological non-suppression (VL>50 copies/mL; comprising 79 (36%) with >500 copies/mL, 68 (31%) with >1000 copies/mL, and 32 (15%) with >10000 copies/mL). For each of the four indicators of SES, socio-economic disadvantage was strongly associated with virological non-suppression (Figure 7.3). In addition, individuals with non-fluent English reading ability and those who had children had a greater prevalence of virological non-suppression. There was also weak evidence of an increased prevalence of virological non-suppression among those living in the UK for over five years but not born in the UK, those with lowest supportive network and those without a current partner. The demographic factors associated with virological non-suppression were being an MSW or woman compared to MSM, black African or other compared to white ethnicity, and younger age.

Figure 7.3: Prevalence of virological non-suppression (VL >50 copies/mL) by socio-economic and demographic factors [a]



[a] Cross-sectional analysis among 2405 respondents who had started antiretroviral therapy (ART) >6 months prior to completion of the questionnaire; [b] Cochran-Armitage test for trend; [c] Chi square test.

The markers of lower SES: financial hardship, non-employment, non-homeownership, and non-university education all remained strongly associated with virological non-suppression after adjustment for demographic factors (Table 7.3). There was a marked trend between greater prevalence of virological non-suppression and increasing financial hardship and housing instability. In terms of the social circumstance factors, lowest supportive network and not having a current partner were associated with increased prevalence of virological non-suppression in the model adjusted for demographic factors. English reading ability and having children were not associated with virological non-suppression after accounting for demographic factors.

Table 7.3: Cross-sectional associations of socio-economic factors and social circumstances with virological non-suppression [a] (N=2405)

Factors [b]			**Unadjusted**			**Adjusted for gender/sexual orientation and age**		
		N	aPR	95% CI	P-value[c]	aPR	95% CI	P-value[c]
Enough money for basic needs? (Financial hardship)	Always	1038	1		<.0001 [d]	1		<.0001 [d]
	Mostly	627	1.63	1.15, 2.30		1.57	1.11, 2.22	
	Sometimes	412	2.06	1.44, 2.95		1.87	1.29, 2.72	
	No	290	2.68	1.87, 3.86		2.42	1.67, 3.51	
Employed	Yes	1302	1		<.0001	1		<.0001
	No	1049	1.85	1.42, 2.41		1.98	1.51, 2.61	
Housing status	Homeowner	852	1		<.0001 [d]	1		<.0001 [d]
	Renting	1286	2.39	1.69, 3.39		2.12	1.49, 3.02	
	Unstable	230	3.70	2.42, 5.67		3.04	1.97, 4.68	
University	Yes	977	1		0.0004	1		0.0005
	No	1370	1.63	1.23, 2.16		1.62	1.22, 2.14	
Time in UK	Born in UK	1329	1		0.083	1		0.076
	>5 years	899	1.30	1.00, 1.69		1.01	0.76, 1.35	
	≤5 years	98	0.75	0.34, 1.67		0.51	0.23, 1.14	
English reading ability	Born in UK	1329	1		0.036	1		0.11
	Fluent	825	1.09	0.82, 1.45		0.86	0.64, 1.17	
	Not fluent	182	1.89	1.29, 2.78		1.40	0.91, 2.16	
Supportive network	Most	762	1		0.071 [d]	1		0.049 [d]
	Medium	1273	1.07	0.80, 1.44		1.09	0.82, 1.46	
	Least	342	1.49	1.03, 2.15		1.53	1.06, 2.20	
Children	Yes	661	1		0.0053	1		0.14
	No	1729	0.67	0.51, 0.87		0.74	0.49, 1.10	
Partner	Yes	1363	1		0.094	1		0.023
	No	1026	1.25	0.97, 1.61		1.35	1.05, 1.75	

[a] VL >50 copies/mL at the time of the questionnaire; [b] each socio-economic factor considered in a separate model for all results but gender/sexual orientation and age are included in every model, individuals with missing values for explanatory variables were excluded; [c] Chi square test; [d] test for trend. PR=Prevalence Ratio; aPR=adjusted Prevalence Ratio.

7.4.3.1 *ART non-adherence and virological non-suppression*

ART non-adherence was associated with 2.37 times higher prevalence of virological non-suppression (95% CI: 1.84, 3.07; p<0.0001), adjusted for demographic factors.

7.4.4 **Participant characteristics – longitudinal analyses**

The longitudinal association between socio-economic factors and virological rebound was considered in a subset of the 2186/2405 (91%) participants who had a VL ≤50 copies/mL at the time of the questionnaire (baseline). Of these, 1740 (80%) had linked clinic data and at least one follow-up VL measurement. These individuals were followed for 3818 person-years with a median 2.4 (range: 0.01-3.31, IQR: 2.0-2.7) years of follow-up and a median six (range: 1-25, IQR: 5-8) VL measurements per person. During this period eight (<1%) individuals were known to have died. The characteristics at baseline of the 1740 participants are summarised in Table 7.1.

7.4.5 **SES and virological rebound**

To justify the use of time-to-event analysis I considered whether the median number of VL measurements during follow-up differed according socio-economic and social circumstances factors (Table 7.4). For most factors, there were no differences in frequency of measurement, however, individuals who were not employed, reported a medium or least supportive network, did not have a partner at the time of the questionnaire, and who had children had a greater median number of VL measurements over follow-up. However, this is unlikely to have biased the results to any great extent since the maximum difference between the groups across all of the socio-economic factors was 0.2 VL measurements per year.

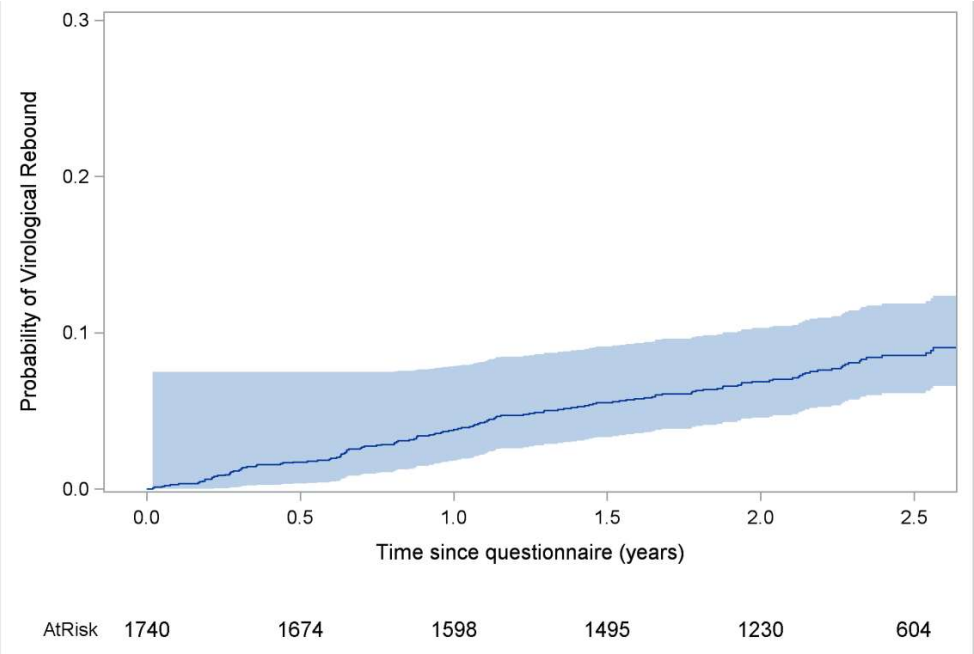
Table 7.4: Median number of VL measurements during follow-up by socio-economic factor

Factors		Number of VL measurements over follow-up		
		Median	**IQR [a]**	**P-value[b]**
Enough money for basic needs? (Financial hardship)	Always	2.73	2.17, 3.33	0.88
	Mostly	2.75	2.17, 3.47	
	Sometimes	2.82	2.12, 3.45	
	No	2.76	2.30, 3.52	
Employed	Yes	2.68	2.11, 3.27	<.0001
	No	2.88	2.28, 3.55	
Housing status	Homeowner	2.73	2.16, 3.30	0.53
	Renting	2.76	2.19, 3.48	
	Unstable/ other	2.80	2.14, 3.53	
University education	Yes	2.70	2.11, 3.35	0.12
	No	2.80	2.21, 3.46	
Time in UK	Born in UK	2.79	2.22, 3.40	0.074
	In UK >5 years	2.69	2.08, 3.35	
	In UK ≤5 years	2.85	2.33, 3.61	
English reading ability	Born in UK	2.79	2.22, 3.40	0.11
	Fluent	2.69	2.10, 3.34	
	Not fluent	2.84	2.10, 3.56	
Supportive network	Most support	2.68	2.12, 3.27	0.013
	Medium support	2.81	2.20, 3.43	
	Least support	2.79	2.27, 3.60	
Children	Yes	2.62	2.05, 3.34	0.0045
	No	2.78	2.21, 3.43	
Partner	Yes	2.69	2.12, 3.33	0.0040
	No	2.84	2.26, 3.48	

[a] IQR = interquartile range; [b] Kruskal-Wallis test.

Over follow-up, 139 (8%) individuals experienced virological rebound, with a rate of 3.6/100 person-years (95% CI 3.0, 4.2). By 12 and 24 months of follow-up the Kaplan Meier estimates (95% CI) of virological rebound were 3.9% (3.0, 4.8) and 7.0% (5.7, 8.2), respectively (Figure 7.4).

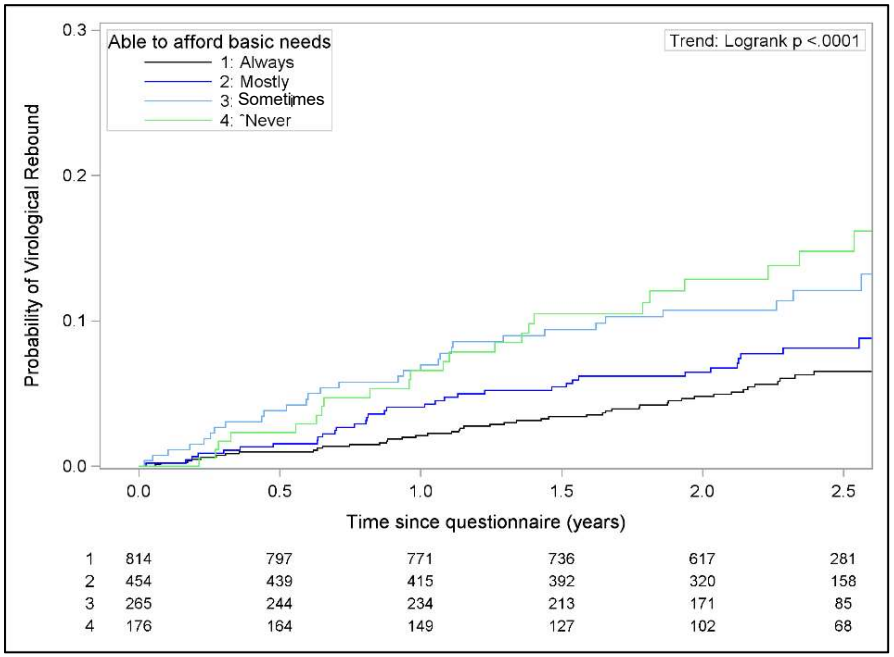
Figure 7.4: Kaplan-Meier plot of time until virological rebound (VL >200 copies/mL) [a] with 95% confidence bands [b]



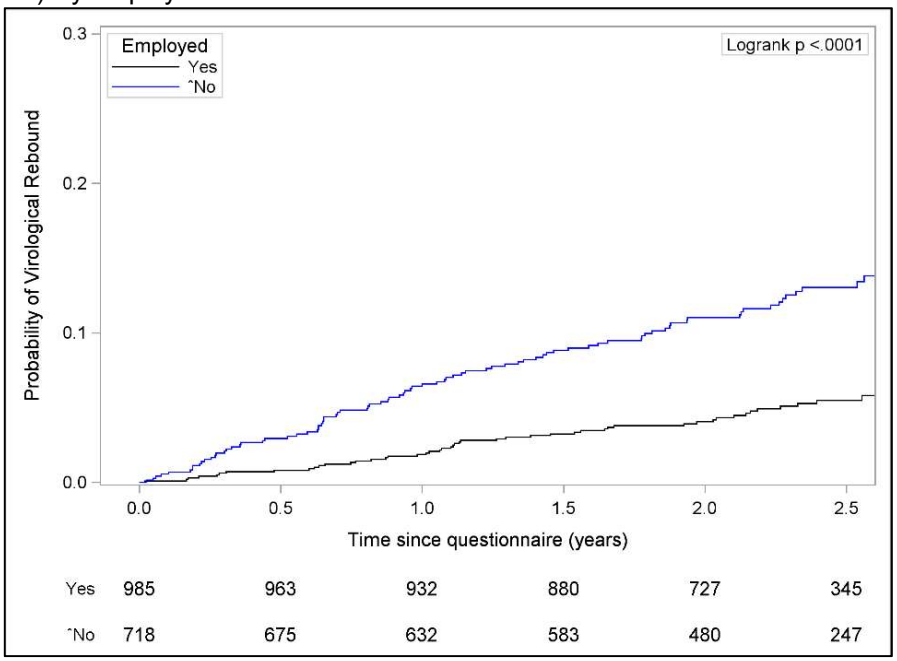
[a] Longitudinal analysis among N=1740 respondents with VL <50 copies/mL at the time of the questionnaire; [b] confidence bands displayed by the shaded area.

Figure 7.5: Kaplan-Meier plot of time until virological rebound (VL >200 copies/mL) [a]

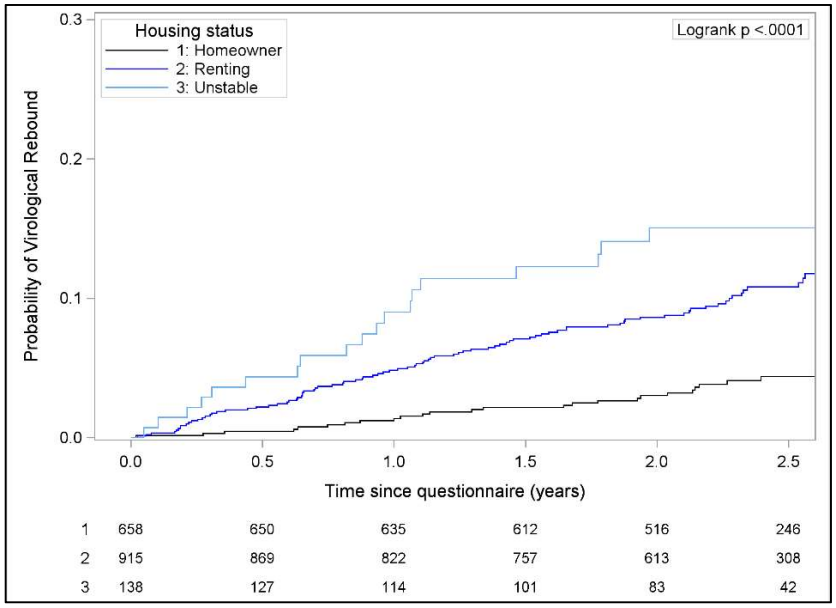
a) By ability to afford basic needs (financial hardship) at baseline



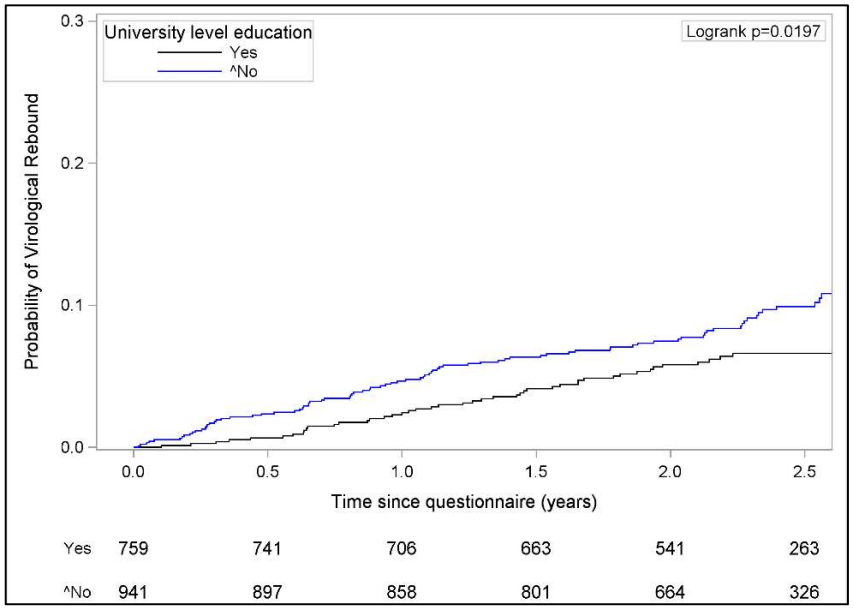
b) By employment status at baseline



c) By housing status at baseline



d) By university education at baseline



[a] Longitudinal analysis among N=1740 respondents with VL <50 copies/mL at the time of the questionnaire. Individuals with missing values were excluded. Numbers provided indicate the number of individuals at risk.

In unadjusted Cox regression analyses, increased financial hardship, non-employment, and rented or unstable housing status were strongly predictive of increased rate of virological rebound (Table 7.5). Although the effect size was not as large, non-university education was also associated with increased rebound rate. In addition, decreased supportive network, having children, and not having a partner were associated with a higher rate of virological rebound. However, there was no evidence that time in the UK and English reading ability were associated with rebound. The pattern of associations remained, with some attenuation for most factors, after adjustment for gender/sexual orientation and age. For employment, time in the UK, supportive network, and current partner the effect sizes increased after adjustment, indicating a possible interaction between these and the demographic factors.

Table 7.5: Longitudinal associations of socio-economic factors and social circumstances with virological rebound [a] (N=1740)

Factors [b]		N	Rate [c]	Unadjusted			Adjusted for gender/sexual orientation and age		
				HR	95% CI	P-value[d]	aHR	95% CI	P-value[d]
Enough money for basic needs? (Financial hardship)	Always	814	2.49	1		<.0001 [e]	1		0.0005 [e]
	Mostly	454	3.64	1.47	0.95, 2.27		1.34	0.87, 2.09	
	Sometimes	265	5.60	2.25	1.43, 3.55		1.83	1.14, 2.95	
	No	176	6.95	2.78	1.71, 4.53		2.30	1.39, 3.81	
Employed	Yes	985	2.26	1		<.0001	1		<.0001
	No	718	5.78	2.56	1.81, 3.62		2.87	2.00, 4.10	
Housing status	Homeowner	658	1.70	1		<.0001 [e]	1		<.0001 [e]
	Renting	915	4.76	2.80	1.81, 4.32		2.33	1.49, 3.65	
	Unstable/ other	138	6.95	4.11	2.27, 7.42		3.18	1.73, 5.85	
University education	Yes	759	2.79	1		0.021	1		0.025
	No	941	4.24	1.52	1.07, 2.17		1.50	1.05, 2.15	
Time in UK	Born in UK	983	3.09	1		0.11	1		0.55
	In UK >5 years	635	4.47	1.44	1.02, 2.04		1.03	0.70, 1.53	
	In UK ≤5 years	68	2.96	0.95	0.35, 2.59		0.58	0.21, 1.63	
English reading ability	Born in UK	983	3.09	1		0.14	1		0.94
	Fluent	595	4.35	1.40	0.98, 2.00		1.00	0.68, 1.48	
	Not fluent	114	4.43	1.43	0.74, 2.78		0.89	0.44, 1.81	
Supportive network	Most support	562	3.07	1		0.070 [e]	1		0.050 [e]
	Medium support	930	3.68	1.20	0.81, 1.77		1.19	0.81, 1.76	
	Least support	227	5.04	1.63	0.98, 2.72		1.72	1.03, 2.87	
Children	Yes	426	6.03	1		<.0001	1		0.015
	No	1305	2.91	0.49	0.34, 0.68		0.54	0.33, 0.89	
Partner	Yes	997	2.96	1		0.0081	1		0.0011
	No	731	4.65	1.57	1.12, 2.19		1.75	1.25, 2.45	

[a] Self-reported ART non-adherence: ≥2 consecutive missed days of ART in the past 3 months or ≥1 missed dose in the last 2 weeks; [b] each socio-economic factor considered in a separate model for all results but gender/sexual orientation and age are included in every model, individuals with missing values for explanatory variables were excluded; [c] Chi square test; [d] test for trend. PR=Prevalence Ratio; aPR=adjusted Prevalence Ratio.

7.4.5.1 *ART non-adherence and virological rebound*

Individuals who self-reported ART non-adherence at baseline had over three times the rate of virological rebound compared to individuals who did not (aHR=3.11, 95% CI: 2.20, 4.38; p<0.0001, adjusted for demographic factors).

7.4.6 Association of SES factors with non-adherence and virological outcomes among subgroups white MSM and black African heterosexuals

7.4.6.1 *SES and ART non-adherence - subgroup analyses*

In the subgroup of white MSM, 1665 individuals met the inclusion criteria for the ART non-adherence analyses, of whom 490 (29%) reported ART non-adherence. Similarly, to the main analysis, in this subgroup all four measures of poorer SES were associated a greater prevalence of ART non-adherence in unadjusted analyses and analyses adjusted for age (Table 7.6).

In the subgroup of black African MSW and women, 195/493 (40%) reported ART non-adherence. In this subgroup, there was a trend of greater prevalence of ART non-adherence with increasing financial hardship and increasing housing instability (Table 7.6). However, there was no association between the other two socio-economic factors and non-adherence.

Table 7.6: Cross-sectional associations of socio-economic factors and social circumstances with ART non-adherence – subgroup analyses [a] [b]

Factors [c]		White MSM only (N=1665)							Black African men and women only (N=493)						
			Unadjusted			Adjusted for age				Unadjusted			Adjusted for age		
		N	PR	95% CI	P-value [d]	aPR	95% CI	P-value [d]	N	PR	95% CI	P-value [d]	aPR	95% CI	P-value [d]
Enough money for basic needs? (Financial hardship)	Always	899	1		<.0001 [e]	1		<.0001 [e]	86	1		0.030 [e]	1		0.030 [e]
	Mostly	450	1.48	1.24, 1.76		1.47	1.23, 1.75		102	1.20	0.80, 1.81		1.20	0.79, 1.80	
	Sometimes	195	1.88	1.54, 2.29		1.84	1.51, 2.25		163	1.42	0.98, 2.05		1.43	0.99, 2.06	
	No	120	1.47	1.12, 1.94		1.45	1.10, 1.90		136	1.44	0.99, 2.09		1.43	0.98, 2.08	
Employed	Yes	999	1		0.0070	1		0.0003	229	1		0.42	1		0.38
	No	658	1.23	1.06, 1.43		1.34	1.15, 1.56		255	1.10	0.88, 1.37		1.10	0.88, 1.38	
Housing status	Homeowner	743	1		0.0002 [e]	1		0.0018 [e]	37	1		0.0088 [e]	1		0.012 [e]
	Renting	814	1.27	1.09, 1.49		1.23	1.04, 1.45		351	1.81	0.96, 3.38		1.79	0.95, 3.35	
	Unstable/ other	106	1.57	1.21, 2.05		1.50	1.14, 1.97		104	2.18	1.14, 4,16		2.14	1.12, 4.08	
University education	Yes	722	1		0.0040	1		0.0027	185	1		0.36	1		0.34
	No	938	1.25	1.07, 1.46		1.26	1.08, 1.47		294	0.90	0.72, 1.13		0.89	0.71, 1.12	

[a] Cross-sectional analysis among respondents who self-reported being on ART at the time of the questionnaire; [b] ART non-adherence: self-reported ≥2 consecutive missed days of ART in the past 3 months or ≥1 missed dose in the last 2 weeks; [c] each socio-economic factor considered in a separate model for all results, individuals with missing values for socio-economic factors were excluded; [d] Chi square test; [e] test for trend; PR=Prevalence Ratio; aPR=adjusted Prevalence Ratio.

7.4.6.2 *SES and virological non-suppression - subgroup analyses*

Of the 1498 white MSM participants, 112 (7%) had a VL >50 copies/mL at the time of the questionnaire. All four measures of poorer SES were associated with higher levels of virological non-suppression in unadjusted analyses and after adjustment for age (Table 7.7).

Of the 452 black African MSW and women, 57 (13%) had a VL >50 copies/mL at the time of the questionnaire. None of the socio-economic factors had a strong association with virological non-suppression; however, there was some evidence that renting or unstable housing status were associated with a higher prevalence of virological non-suppression (Table 7.7).

Table 7.7: Cross-sectional associations of socio-economic factors and social circumstances with virological non-suppression – subgroup analyses [a b]

Factors [c]		White MSM only (N=1498)						Black African men and women only (N=452)					
			Unadjusted			Adjusted for age			N	Unadjusted			Adjusted for age		
		N	PR	95% CI	P-value [d]	aPR	95% CI	P-value [d]		PR	95% CI	P-value [d]	aPR	95% CI	P-value [d]
Enough money for basic needs? (Financial hardship)	Always	813	1		0.0041 [e]	1		0.0055 [e]	81	1		0.25 [e]	1		0.19 [e]
	Mostly	407	1.48	0.96, 2.26		1.45	0.95, 2.23		94	1.29	0.56, 3.01		1.27	0.55, 2.94	
	Sometimes	172	2.06	1.25, 3.38		2.00	1.22, 3.28		148	1.16	0.52, 2.58		1.19	0.54, 2.58	
	No	105	2.02	1.11, 3.69		1.95	1.07, 3.56		125	1.62	0.75, 3.50		1.67	0.79, 3.50	
Employed	Yes	887	1		0.0021	1		0.0002	212	1		0.28	1		0.21
	No	603	1.79	1.25, 2.57		2.12	1.47, 3.08		232	1.31	0.80, 2.16		1.37	0.83, 2.24	
Housing status	Homeowner	677	1		<.0001 [e]	1		0.0001 [e]	36	1		0.059 [e]	1		0.081 [e]
	Renting	731	2.13	1.41, 3.23		1.99	1.32, 3.01		323	2.17	0.55, 8.63		2.15	0.55, 8.35	
	Unstable/ other	88	3.33	1.81, 6.15		3.06	1.67, 5.62		92	3.13	0.76, 12.93		2.87	0.72, 11.52	
University education	Yes	650	1		0.0008	1		0.0006	173	1		0.84	1		0.59
	No	844	1.90	1.28, 2.83		1.93	1.30, 2.88		266	1.05	0.63, 1.75		1.14	0.69, 1.89	

[a] Cross-sectional analysis among 1498 respondents who had started ART >6 months prior to completion of the questionnaire; [b] virological suppression: VL >50 copies/mL at the time of the questionnaire; [c] each socio-economic factor considered in a separate model for all results, individuals with missing values for socio-economic factors were excluded; [d] Chi square test; [e] test for trend; PR=Prevalence Ratio; aPR=adjusted Prevalence Ratio.

7.4.6.3 *SES and virological rebound - subgroup analyses*

There were 1131 white MSM with VL ≤50 copies/mL at the time of the questionnaire with at least one follow-up VL measurement, of whom 70 (6%) had virological rebound in 2561 person-years (rate 2.7/100 person-years; 95% CI 2.4, 2.9). In this subgroup, there was a 93% higher HR for virological rebound among individuals who reported that they only sometimes had enough money for their basic needs compared to individuals who reported that they always did (in model adjusted for age), however, there was not an increasing trend with financial hardship (Table 7.8). Not being employed, living in rented accommodation, and not having a university education were predictive of a greater rate of virological rebound. However, unstable housing status was not associated with virological rebound in this subgroup.

In the subgroup of black African MSW and women, 34/276 (12%) individuals had virological rebound in 561 person-years (rate 6.1/100 person-years; 95% CI 5.3, 6.8). In this subgroup, individuals who could not always afford their basic needs, non-employed individuals, and those with unstable housing had over twice the HR of rebound compared to those who could always afford basic needs, were employed, and homeowners, respectively, after adjustment for gender and age (Table 7.8).

Table 7.8: Longitudinal associations of socio-economic factors and social circumstances with virological rebound - subgroup analyses [a b]

Factors [c]		White MSM only (N=1131)							Black African men and women only (N=276)						
			Unadjusted			Adjusted for age				Unadjusted			Adjusted for age		
		Rate [d]	HR	95% CI	P-value [e]	aHR	95% CI	P-value [e]	Rate [d]	HR	95% CI	P-value [e]	aHR	95% CI	P-value [e]
Enough money for basic needs? (Financial hardship)	Always	2.41	1		0.21 [f]	1		0.27 [f]	2.96	1		0.20 [f]	1		0.18 [f]
	Mostly	2.73	1.14	0.65, 2.00		1.12	0.63, 1.97		6.34	2.22	0.59, 8.39		2.07	0.55, 7.87	
	Sometimes	4.83	2.00	1.04, 3.85		1.93	1.00, 3.71		7.02	2.45	0.70, 8.61		2.38	0.67, 8.39	
	No	2.53	1.05	0.37, 2.94		0.99	0.35, 2.79		7.20	2.50	0.69, 9.10		2.49	0.68, 9.07	
Employed	Yes	2.05	1		0.0074	1		0.0002	3.54	1		0.028	1		0.017
	No	3.91	1.90	1.19, 3.04		2.55	1.56, 4.15		8.51	2.36	1.10, 5.05		2.55	1.18, 5.47	
Housing status	Homeowner	1.51	1		0.013 [f]	1		0.047 [f]	5.66	1		0.029[f]	1		0.039 [f]
	Renting	4.01	2.47	1.46, 4.15		2.22	1.30, 3.78		4.74	0.79	0.23, 2.67		0.79	0.23, 2.68	
	Unstable/ other	1.56	0.97	0.23, 4.15		0.87	0.20, 3.73		13.23	2.28	0.64, 8.19		2.17	0.60, 7.80	
University education	Yes	1.84	1		0.011	1		0.0079	7.57	1		0.22	1		0.31
	No	3.53	1.93	1.16, 3.19		1.98	1.20, 3.29		4.96	0.65	0.33, 1.29		0.70	0.35, 1.39	

[a] Longitudinal analysis among respondents with VL <50copies/mL at the time of the questionnaire; [b] virological rebound: a subsequent VL >200copies/mL; [c] each baseline socio-economic factor considered in a separate model for all results, individuals with missing values for socio-economic factors were excluded; [d] per 100 person-years; [e] Chi square test; [f] test for trend; HR= Hazard Ratio; aHR=adjusted Hazard Ratio.

7.4.7 **ART non-adherence as a mediator of the association between SES and virological response to ART**

In this analysis, non-adherence was added as an additional independent variable together with gender/sexual orientation and age, in the modified Poisson regression model for the main cross-sectional analysis of virological non-suppression. This was done in order to assess to what extent this measure could account for any associations of socio-economic factors with virological non-suppression. The results are displayed in the first column of Table 7.9. The association between each of the four markers of SES and virological non-suppression remained after adjustment for ART non-adherence; however, all associations were attenuated further (by 9-45% on top of the attenuation by adjusting for gender/sexual orientation and age).

Similarly, the Cox Proportional hazards model for virological rebound was additionally adjusted for self-reported ART non-adherence at baseline (results shown in second column of Table 7.9). The adjustment for ART non-adherence did not fully explain the associations between virological rebound and the socio-economic factors, but associations were further attenuated in each case (by 8-48%).

Table 7.9: Associations of socio-economic factors and social circumstances with virological non-suppression [a] (N=2405) and virological rebound [b] (N=1740) adjusted for gender/sexual orientation, age, and ART non-adherence [c]

Factors [d]		Virological non-suppression [a]						Virological rebound [b]					
			Adjusted for demographic factors			Additionally adjusted for ART non-adherence			Adjusted for demographic factors			Additionally adjusted for ART non-adherence	
		N	aPR	95% CI	P-value [e]	aPR	95% CI	P-value [e]	N	aHR	95% CI	P-value [e]	aHR	95% CI	P-value [e]
Enough money for basic needs? (Financial hardship)	Always	1038	1		<.0001 [d]	1		<.0001 [f]	814	1		0.0005 [e]	1		0.018 [f]
	Mostly	627	1.57	1.11, 2.22		1.44	1.02, 2.04		454	1.34	0.87, 2.09		1.22	0.79, 1.90	
	Sometimes	412	1.87	1.29, 2.72		1.56	1.08, 2.27		265	1.83	1.14, 2.95		1.44	0.89, 2.32	
	No	290	2.42	1.67, 3.51		2.04	1.40, 2.98		176	2.30	1.39, 3.81		1.82	1.09, 3.04	
Employed	Yes	1302	1		<.0001	1		<.0001	985	1		<.0001	1		<.0001
	No	1049	1.98	1.51, 2.61		1.82	1.39, 2.37		718	2.87	2.00, 4.10		2.67	1.87, 3.82	
Housing status	Homeowner	852	1		<.0001 [d]	1		<.0001 [f]	658	1		<.0001 [e]	1		0.0002 [f]
	Renting	1286	2.12	1.49, 3.02		1.95	1.37, 2.78		915	2.33	1.49, 3.65		2.18	1.39, 3.41	
	Unstable	230	3.04	1.97, 4.68		2.59	1.67, 4.02		138	3.18	1.73, 5.85		2.74	1.49, 5.04	
University	Yes	977	1		0.0005	1		0.0016	759	1		0.025	1		0.053
	No	1370	1.62	1.22, 2.14		1.53	1.16, 2.03		941	1.50	1.05, 2.15		1.42	1.00, 2.03	

[a] Cross-sectional analysis, virological non-suppression= VL >50 copies/mL at the time of the questionnaire; [b] Longitudinal analysis, virological rebound= VL <50copies/mL at the time of the questionnaire followed by a subsequent VL >200copies/mL; [c] self-reported ≥2 consecutive missed days of ART in the past 3 months or ≥1 missed dose in the last 2 weeks; [d] each socio-economic factor considered in a separate model for all results but gender/sexual orientation, age and ART non-adherence are included in every model, individuals with missing values for explanatory variables were excluded; [e] Chi square test; [f] test for trend. aPR=adjusted Prevalence Ratio; aHR=adjusted Hazard Ratio.

7.4.8 **Sensitivity analyses**

7.4.8.1 ***SES and ART non-adherence - sensitivity analysis***

In a sensitivity analysis, the 65 individuals who had been on ART previously but were not on ART at the time of the questionnaire, were defined as non-adherent. After the inclusion of these individuals, 938/2769 (34%; 95% CI: 32%, 36%) were defined as non-adherent to ART. The results of this analysis showed associations between all four markers of lower SES and greater prevalence of ART non-adherence, similar to the main analysis (Table 7.10).

Table 7.10: Sensitivity analysis: individuals previously on ART defined as non-adherent [a]

Factors [b]			**Unadjusted**			**Adjusted for gender/sexual orientation and age**		
		N	**PR**	**95% CI**	**P-value[c]**	**aPR**	**95% CI**	**P-value[c]**
Enough money for basic needs? (Financial hardship)	Always	1192	1		<.0001 [d]	1		<.0001 [d]
	Mostly	720	1.43	1.24, 1.64		1.41	1.22, 1.62	
	Sometimes	477	1.83	1.59, 2.11		1.78	1.54, 2.05	
	No	337	1.79	1.54, 2.09		1.72	1.47, 2.02	
Employed	Yes	1506	1		<.0001	1		<.0001
	No	1203	1.25	1.13, 1.39		1.31	1.18, 1.46	
Housing status	Homeowner	954	1		<.0001 [d]	1		<.0001 [d]
	Renting	1493	1.48	1.30, 1.68		1.37	1.20, 1.57	
	Unstable	282	1.79	1.51, 2.12		1.61	1.35, 1.93	
University	Yes	1119	1		0.0037	1		0.0054
	No	1587	1.17	1.05, 1.31		1.17	1.05, 1.30	

[a] ART non-adherence: (i) previously on ART but not at the time of the questionnaire, or (ii) self-reported ≥2 consecutive missed days of ART in the past 3 months or ≥1 missed dose in the last 2 weeks; [b] each socio-economic factor considered in a separate model for all results but gender/sexual orientation and age are included in every model, individuals with missing values for explanatory variables were excluded; [c] Chi square test; [d] test for trend.
PR=Prevalence Ratio; aPR=adjusted Prevalence Ratio.

7.4.8.2 *SES and virological non-suppression - sensitivity analysis*

The analysis of the association between virological non-suppression and socio-economic factors was repeated using a VL >200 copies/mL at the time of the questionnaire as the definition of non-suppression rather than >50 copies/mL. Using this definition 115/2405 individuals (5%; 95% CI: 4%, 6%) were virologically non-suppressed. The results were consistent with those of the main analysis (Table 7.11). All four markers of socio-economic disadvantage were strongly associated with a higher prevalence of VL >200 copies/mL, even after adjustment for gender/sexual orientation and age.

Table 7.11: Sensitivity analysis: virological non-suppression defined as VL >200 copies/mL (N= 2405)

Factors [a]			**Unadjusted**			**Adjusted for gender/sexual orientation and age**		
		N	**PR**	**95% CI**	**P-value**[b]	**aPR**	**95% CI**	**P-value**[b]
Enough money for basic needs? (Financial hardship)	Always	1038	1		<.0001 [c]	1		<.0001 [c]
	Mostly	627	1.34	0.80, 2.24		1.30	0.77, 2.19	
	Sometimes	412	2.52	1.55, 4.09		2.34	1.39, 3.94	
	No	290	3.12	1.89, 5.14		2.93	1.73, 4.94	
Employed	Yes	1302	1		<.0001	1		<.0001
	No	1049	2.35	1.60, 3.45		2.60	1.74, 3.91	
Housing status	Homeowner	852	1		<.0001 [c]	1		0.0002 [c]
	Renting	1286	3.08	1.84, 5.16		2.70	1.60, 4.54	
	Unstable/ other	230	3.92	2.05, 7.49		3.08	1.58, 6.03	
University education	Yes	977	1		0.0003	1		0.0003
	No	1370	2.00	1.33, 3.00		2.00	1.33, 3.00	

[a] Each socio-economic factor considered in a separate model for all results, individuals with missing values for socio-economic factors were excluded; [b] Chi square test; [c] test for trend; PR=Prevalence Ratio; aPR=adjusted Prevalence Ratio.

7.4.8.3 *SES and virological rebound - sensitivity analyses*

In the first longitudinal sensitivity analysis, virological rebound was redefined as a VL ≤50 copies/mL at baseline followed by two consecutive VL measurements >200 copies/mL among individuals with at least two VL measurements following the date of the questionnaire. Of 1717 individuals included in this analysis, 75 (4%) had virological rebound during follow-up. The associations between the socio-economic factors and virological rebound were consistent with those in the main analysis, although the effect sizes were generally larger (Table 7.12).

In the second longitudinal sensitivity analysis, virological rebound was defined in the same way as in the main analysis (VL≤50 copies/mL at baseline and one subsequent VL>200 copies/mL), however, additionally individuals were considered to have experienced virological rebound six months after their last VL measurement if they were LTFU. Individuals were classified as LTFU if they had had at least one VL measurement after the date of the questionnaire but their latest VL measurement was over eighteen months prior to the administrative censoring date, which differed by clinical centre. These were April 2014 for Brighton, January 2015 for Eastbourne, March 2013 for Homerton, December 2013 for Mortimer Market, October 2015 for Newham, and May 2014 for the Royal Free. Of 1740 individuals, 226 (13%) had virological rebound during follow-up. Again, the results of this sensitivity analysis were consistent with the main analyses (Table 7.12).

Table 7.12: Sensitivity analyses where virological rebound was the outcome

Factors [a]		N	Rate [b]	Unadjusted			Adjusted for gender/sexual orientation and age		
				HR	95% CI	P-value[c]	aHR	95% CI	P-value[c]
Virological rebound defined as confirmed VL measurements >200 copies/mL (N=1717)									
Enough money for basic needs? (Financial hardship)	Always	810	1.17	1		<.0001 [d]	1		0.0007 [d]
	Mostly	448	2.30	1.98	1.10, 3.54		1.80	1.00, 3.24	
	Sometimes	258	1.92	1.64	0.79, 3.38		1.30	0.62, 2.75	
	No	170	5.21	4.38	2.37, 8.10		3.60	1.90, 6.83	
Employed	Yes	975	1.12	1		<.0001	1		<.0001
	No	705	3.20	2.86	1.77, 4.63		3.29	2.01, 5.40	
Housing status	Homeowner	654	0.78	1		<.0001 [d]	1		0.0025 [d]
	Renting	899	2.71	3.50	1.87, 6.54		2.81	1.48, 5.33	
	Unstable/ other	135	3.19	4.17	1.76, 9.90		3.02	1.24, 7.32	
University education	Yes	749	1.11	1		0.0016	1		0.0016
	No	928	2.59	2.33	1.38, 3.92		2.33	1.38, 3.94	
Individuals lost to follow-up considered as having virological rebound (N=1740) [e]									
Enough money for basic needs? (Financial hardship)	Always	814	3.97	1		<.0001 [d]	1		<.0001 [d]
	Mostly	454	5.79	1.46	1.03, 2.06		1.35	0.95, 1.90	
	Sometimes	265	8.36	2.11	1.46, 3.04		1.73	1.18, 2.53	
	No	176	11.89	3.02	2.08, 4.39		2.49	1.69, 3.67	
Employed	Yes	985	3.98	1		<.0001	1		<.0001
	No	718	8.66	2.18	1.67, 2.85		2.42	1.83, 3.19	
Housing status	Homeowner	658	2.60	1		<.0001 [d]	1		<.0001 [d]
	Renting	915	7.61	2.92	2.06, 4.14		2.43	1.70, 3.48	
	Unstable/ other	138	11.39	4.38	2.75, 6.97		3.41	2.11, 5.49	
University education	Yes	759	4.87	1		0.037	1		0.047
	No	941	6.50	1.34	1.02, 1.76		1.32	1.00, 1.74	

[a] Each socio-economic factor considered in a separate model for all results, individuals with missing values for socio-economic factors were excluded; [b] per 100 person-years; [c] Chi square test; [d] test for trend; [e] LTFU defined as consented longitudinal linkage and ≥1 VL measurement after questionnaire date but latest follow-up VL over eighteen months before administrative censoring date, date of rebound for these individuals is the date of but latest follow-up VL plus six months; HR= Hazard Ratio; aHR=adjusted Hazard Ratio.

7.5 **Discussion**

7.5.1 **Summary of results**

- The present study is the first to assess the impact of SES on virological outcomes among people treated for HIV in the UK. In this setting with universal free access to healthcare, and high levels of treatment success, all four markers of poorer SES considered (financial hardship, non-employment, rented/unstable housing status, and non-university education) were strongly associated with ART non-adherence and virological non-suppression.
- Furthermore, each marker of poorer SES was predictive of subsequent virological rebound among those who had achieved virological suppression on ART at baseline. Additional social circumstance factors were also found to be associated with treatment adherence and response. Individuals living in the UK for over five years but not born in the UK, and individuals with non-fluent English reading ability had a greater prevalence of ART non-adherence compared to individuals born in the UK, and there was some evidence that they had a greater prevalence of virological non-suppression too. In addition, less supportive network, having children and not having a current partner were associated with a greater prevalence of ART non-adherence and virological non-suppression, and predictive of virological rebound.
- There were strong associations between socio-economic factors and ART non-adherence, and between non-adherence and poorer virological response. This suggests that, as might be expected, at least part of the observed associations between lower SES and virological non-suppression were mediated through ART non-adherence. The associations between socio-economic factors and virological outcomes were attenuated to some extent when adjusted for non-adherence, which lends some support for non-adherence as a mechanism.

7.5.2 **Interpretation of results**

These results from a setting of universal health care suggest that the implications of poorer SES on treatment outcomes go beyond inability to pay for treatment and associated healthcare costs, and operate strongly even amongst those who are accessing, and engaged with, clinical care. Socio-economic effects on outcome were also apparent after adjustment for demographic factors and specifically among the white MSM subgroup and the black African MSW and women subgroup. This showed that they were not solely a feature of the diverse demographic composition of the HIV-positive population in the UK.

Overall, virological suppression rates are high among people on ART in the UK[631]. This was evident in the present study: 91% of respondents on ART for at least six months had a VL ≤50 copies/mL and 95% had a VL ≤200 copies/mL at the time of the questionnaire. Of those with VL ≤50 copies/mL and available follow-up, only 8% experienced virological rebound after a median 2.3 years. It is worth noting that this was a population with an average time on ART at the time of the questionnaire of eight years, and so one might have expected better virological outcomes compared to individuals who had all recently started treatment[334]. Though there was substantial variation in the prevalence of virological suppression by socio-economic factors, across all subgroups considered the proportion with VL >50 copies/mL never exceeded 20%, indicating that, even among those of lower SES, the majority were successfully treated.

Associations were apparent both for education and for the other markers of SES, but there was some evidence that associations were stronger for markers of current financial status (money for basic needs, housing and employment) than for level of education. These results provide evidence of the importance of current socio-economic disadvantage in determining virological outcomes of ART.

It is important to appreciate the apparent impact of socio-economic factors on non-adherence, even in the current era of simpler and more tolerable drugs, with the majority of participants on once a day regimens. There are a number of reasons why people with greater levels of social or financial disadvantage may have greater difficulties maintaining ART adherence, including: competing responsibilities, stress and/or worries about work[632], housing, family or social situations[633], unsettled living circumstances, food insecurity (particularly when the ART regimen requires food[401]), increased prevalence of depression and other mental health problems[373;625;634;635], increased medication burden due to other comorbid conditions, stigma and low self-esteem[636], or less knowledge about the importance of adherence[637]. However, it is also worth noting that other studies suggest that part of the effect of SES on virological outcomes may be independent of non-adherence, for example related to: late diagnosis[638;639], lower CD4 count or AIDS at ART initiation[163], prescription/non-prescription drug-drug interactions[640-642], differences in quality of healthcare or experiences of healthcare[643], pharmacokinetics through absence of food[644], and possibly direct biological effects of psychosocial factors[645-647].

The self-reported measure of adherence used in the analyses in this chapter did not explain all of the effect, as with the ART non-adherence measure in Chapter 6 (Section 6.4.4.4). This measurement may not fully capture adherence to treatment

since only a single time-point was considered and it may be subject to social desirability bias. Nonetheless, at least part of the observed associations between lower SES and virological non-suppression were explained by this crude binary measure of adherence.

7.5.3 **Strengths and limitations**

Although these analyses provide evidence that SES disadvantage impacts on non-adherence to ART, they do not help to elucidate the precise mechanisms by which this relationship occurs. Further analyses are required to investigate how exactly socio-economic status effects an individual's ability to adhere to treatment.

There were some limitations in the data collected by the ASTRA questionnaire study. The response rate was 64% and non-responders may differ from responders with regard to socio-economic factors and association with virological outcomes. Thus, there may be a higher prevalence of poorer SES among non-responders and the associations between SES and VL outcomes may be under or overestimated. Several participants had missing data for some of the variables included in the analysis. The use of complete case analysis could have introduced bias if the missing data mechanism was not missing completely at random (MCAR). However, since the proportion of individuals with missing data was low, the bias introduced is likely to be minimal. The age of any children was only asked on the questionnaire for women, and even this had missing data, it was not possible to consider the ages of any children. Furthermore, the questionnaire did not collect data on whether the individual was currently looking after any children. I did not account for whether participants were on first-line or subsequent ART regimens, and the specific regimen used, because these data were not available from the questionnaire. Furthermore, in longitudinal analyses, it would have been useful to assess the effect of adjustment for previous history of ART exposure, previous virological failures, and duration of current virological suppression, however, complete treatment and virological history was not available for a substantial portion of ASTRA participants. Therefore, the analyses presented in this chapter cannot determine whether poorer outcomes among people with socio-economic disadvantage were linked to use of different ART regimens. In the cross-sectional analysis, only association can be studied[648], and it is not possible to rule out the presence of reverse causality for some factors. However, the main findings were reinforced in the longitudinal analysis, which was unlikely to suffer from this bias as SES was measured at the time of the questionnaire, at which point all individuals had virological suppression.

There were also limitations concerning the analysis of ART adherence. The measures of adherence to ART were by self-report, and as such they may have been subject to response bias[649] (refer to Section 1.3.3.3). The measures were also reported at a single point in time and were unlikely to fully capture adherence patterns for an individual. This was especially true in the longitudinal analysis, which required individuals to be virologically suppressed on ART at the time of reporting adherence. Individuals who had previously been on ART but were not on ART at the time of the questionnaire were not included in the main analysis. When these individuals were considered non-adherent in a sensitivity analysis, the prevalence of non-adherence and non-suppression was slightly higher, but socio-economic associations were unchanged. In Section 7.4.7, the method of adjusting for adherence in order to assess whether it mediates the associations between SES and VL outcomes may suffer from the same limitations discussed in Chapter 6 (Section 6.5.3) where a similar method was used. The fact that the socio-economic associations were not fully explained by non-adherence may be due to the inability of the two self-reported baseline measures to completely capture all aspects of recent and subsequent non-adherence, and the potential for both recall and social desirability bias in such measures[650;651].

Longitudinal 'time-to-rebound' analyses are potentially subject to bias if the frequency of VL monitoring differs according to explanatory variables. Although in Chapter 6 time-to-event analyses were not appropriate, for the reasons given in Section 6.3.5, it was more appropriate in the present chapter since the median number of VL measurements during follow-up was reasonably similar across socio-economic subgroups. With more data, longitudinal analysis using fixed time-points analysis would be a useful additional analysis to minimise this particular bias. LTFU was considered as virological rebound in a sensitivity analysis in order to account for differences by SES. It may have been useful to look at a snapshot of LTFU[652], however, there was insufficient follow-up data to conduct this analysis.

The study population had a lower proportion of black African individuals, a lower proportion of individuals who acquired HIV through heterosexual sex, and a greater proportion of MSM than among PLWH in the UK in general[210]. Furthermore, as discussed earlier, the findings of the present analysis are not necessarily generalisable to other European settings including those which may have greater socio-economic disparities (for example Eastern Europe), or a greater proportion of people who inject drugs (PWID). Only 2% of the study population were PWID, however, this group make up a greater proportion of the HIV-positive population in other settings, for example in Eastern Europe and central Asia 51% of new diagnoses in 2014 were PWID. In settings with different healthcare systems to the UK, where HIV treatment may not be

free of charge and thus not as easily accessible to individuals with lower SES, it is conceivable that the association of socio-economic factors on treatment outcomes may be even stronger than that found in the present analysis.

The analyses presented from the ASTRA study do not adjust for study centre. Such adjustment was not considered ideal, given the aims of the thesis, because study centre was confounded with gender/sexual orientation – since for some clinics, the vast majority of patients were MSM and for other clinics, patients were predominately heterosexual men and women. Furthermore, study centre was also confounded with SES; therefore adjusting for it would have removed some socio-economic effects that I wished to measure. Therefore, I took the decision not to adjust for clinic in the analyses for my thesis. Although it would be interesting to assess regional differences in treatment response, this ASTRA study is limited in this respect as 5 out of 8 clinics were in London, and all but one in the south of England. Furthermore, ASTRA policies prohibit publication of clinic-specific comparisons.

7.6 **Conclusions**

In summary, even in a European setting with free access to treatment and overall high rates of treatment success, lower SES substantially influenced HIV treatment outcomes. Emphasis should be placed on supporting adherence of people in these higher risk groups. Socio-economic factors should be taken into account when designing clinical management strategies including linkage to the relevant social agencies. Further research is needed on specific interventions that may reduce socio-economic inequalities in HIV-outcomes.

Chapter 8 Can socio-economic disadvantage explain gender/sexual orientation disparities in ART adherence and virological response to ART in the UK?

8.1 Objectives

- To assess the association of gender/sexual orientation with ART adherence and virological response to ART, using data from the ASTRA study.
- To assess differences in socio-economic factors according to gender/sexual orientation.
- To investigate whether any observed differences in socio-economic disadvantage between MSM, MSW and women were able to explain any observed differences in ART adherence and virological outcomes between the gender/sexual orientation groups.

8.2 Introduction

Previous studies in high-income settings in HIV-positive populations have shown that the prevalence of socio-economic deprivation differs by gender/sexual orientation. In particular, women and MSW on average have poorer socio-economic status (SES) than MSM[323;324;357;364;375]. These differences could have therefore played a part in explaining the observed inequalities by gender/sexual orientation in ART response. In Chapter 7, gender/sexual orientation and socio-economic factors were considered in the same model for virological response, but the focus was on the marginal effect of SES alone. This chapter extended these analyses to explicitly examine the extent to which socio-economic factors differed across gender/sexual orientation groups, and to assess whether such variation in SES 'explained' differences in virological response by gender/sexual orientation.

The issue has previously been addressed in a limited number of studies. Two European studies found some evidence that adjustment for socio-economic factors attenuated differences in virological suppression between gender/sexual orientation groups[126;359] (these were discussed in detail in Section 2.6.1). However, both of these studies adjusted for multiple factors simultaneously, and one also included clinical factors and the other additionally included ART adherence. Therefore, it is difficult to make inferences from these studies regarding whether SES could act as a mediator for gender/sexual orientation and VL response associations. Furthermore, demographic and socio-economic effects on treatment outcomes may not be generalisable across different geographic settings.

In this chapter, I assessed the extent to which differences in ART adherence and virological response to ART between gender/sexual orientation groups were explained by SES and other factors. This was in order to provide insight into likely pathways through which gender/sexual orientation impacts on virological suppression, and thus suggest potential target areas for intervention to improve virological response to ART and reduce inequalities in response.

8.3 **Methods**

8.3.1 **Study design**

This chapter used the same cross-sectional and longitudinal ASTRA study data as for the analyses in Chapter 7.

8.3.2 **Outcomes of interest and inclusion criteria**

In this chapter, the three outcomes and respective entry criteria were identical to those described in Section 7.3.3: ART non-adherence, virological non-suppression and virological rebound.

8.3.3 **Covariate of interest**

The main covariate of interest in this chapter was gender/sexual orientation, categorised as MSM, MSW, and women. As in Chapter 7, sexual orientation was derived from patient-reported sexual orientation (see Section 4.4.2).

8.3.4 **Other covariates**

The same four indicators of SES considered in Chapter 7 were used again here in identical form (see Section 4.4.2 for definitions):

SES factors:

- Ability to afford basic needs (financial hardship with four levels),
- Employed (yes; no),
- Housing status (homeowner; renting; unstable/other),
- University education (yes; no).

Four social circumstance factors, English reading ability, time in the UK, social support, and current partner were considered as in the previous chapter. An additional variable was also derived based on country of birth, with people who were non-UK born categorised according to whether they were born in Europe, Africa or other region. Furthermore, whether or not participants had children was not used because

this measure was exceptionally closely linked to sexual orientation (7% MSM vs. 69% MSW and 74% women reported having children, Spearman's rank coefficient = 0.66) and therefore would necessarily be expected to 'explain' much of the variation in outcomes across gender/sexual orientation groups. As discussed in Chapter 7, it was not possible to derive from the questionnaire the age of children or whether participants were currently looking after children. I also considered markers of mental health and lifestyle. Thus, the following covariates were also considered in this chapter:

Social circumstances factors:

- Country of birth (UK; European; African; other),
- Time in UK (UK-born; >5 years; ≤5 years),
- English reading ability (UK-born; fluent; not fluent),
- Supportive network (most; medium; least),
- Current partner (yes; no).

Mental health factors:

- Major depressive symptoms (yes; no),
- Major or other depressive symptoms (yes; no).

Lifestyle factors:

- Recreational drug use in the last 3 months (yes; no),
- Evidence of alcohol dependency (yes; no).

8.3.5 **Statistical analysis**

8.3.5.1 ***Cross-sectional analyses***

The characteristics of the individuals at the time of the questionnaire were summarised according to gender/sexual orientation and compared using Chi-squared tests.

The prevalence of ART non-adherence and virological non-suppression by gender/sexual orientation and then by each of the other covariates were summarised and compared using the Chi-squared test, or Cochran-Armitage test for trend for ordered categorical variables.

Other analysis methods were initially similar to those used in Chapter 7. Unadjusted and adjusted prevalence ratios (PR) were produced for the association of gender/sexual orientation with ART non-adherence and virological non-suppression using modified Poisson regression. I constructed linear contrasts in order to define pairwise comparisons for MSW vs. MSM, women vs. MSM, and women vs. MSW, but

all came from the same regression model. A number of models were considered to evaluate the effect of adjustment for different socio-economic factors on the association between gender/sexual orientation and non-adherence/virological non-suppression. The first adjusted model included only gender/sexual orientation and age as covariates. Each subsequent model included gender/sexual orientation, age, and each additional socio-economic factor from those listed in Section 8.3.4 in turn. Two additional models included gender/sexual orientation, age, and multiple socio-economic factors: (i) all four socio-economic factors; and (ii) a subset of socio-economic factors selected using stepwise variable selection (with an entry and exit P-value of 0.05). In the stepwise method, a sequence of log-likelihood tests were used to select a subset of the four socio-economic factors for each outcome. In addition, in order to put the results for SES factors into context, each of the social circumstance, mental health and lifestyle factors from Section 8.3.4 were included in a separate model alongside gender/sexual orientation and age. Age was adjusted for in all models to reduce confounding by age, as women attending for HIV care are generally younger than men, and age is a known predictor of ART-adherence and virological suppression on ART[163;455;653-656].

As previously discussed, ART adherence is likely to be on the causal pathway between gender/sexual orientation or SES and lack of treatment response. Thus, in Chapters 6 and 7 ART non-adherence was adjusted for in order to assess the extent to which poorer ART adherence could explain differences in ART response by gender/sexual orientation and SES, respectively. In contrast, adherence was not adjusted for in the present chapter since the aim was to assess how much socio-economic disparities account for gender/sexual orientation differences in treatment response, most of which will likely act through non-adherence.

If the addition of a particular covariate (or set of covariates), to the model that included only gender/sexual orientation and age as covariates, resulted in attenuation of the association between gender/sexual orientation and the outcome in question (i.e. the PR moved closer to one), then this suggested that this covariate (or set of covariates) was “explaining” part of the association. See Section 6.5.3 for the assumptions underlying this.

8.3.5.2 ***Longitudinal analyses***

In longitudinal analyses, Cox proportional hazards regression models were used to generate unadjusted and adjusted hazard ratios (HR) for the association between gender/sexual orientation and time to virological rebound. The strategy of adjustment used in the models was identical to that described in Section 8.3.5.1 .

8.3.6 **Sensitivity analyses**

Two sensitivity analyses were performed: virological non-suppression was defined as VL >200 copies/mL; and individuals who were lost to follow-up (LTFU) were considered as having experienced virological rebound six months after the date of the last available VL measurement (missing=failure approach). See the methods of Chapter 7 for more details.

8.4 **Results**

8.4.1 **Participant characteristics**

There were many differences between the gender/sexual orientation groups in terms of demographics, socio-economic factors, social circumstances, lifestyle, and HIV related factors. Table 8.1 shows the differences in these factors by gender/sexual orientation among individuals included in the ART non-adherence analysis. There were very similar distributions for the study populations for the virological non-suppression and virological rebound analyses also.

As one might expect, the most prevalent mode of HIV acquisition for MSM and women was sex with a man, and for MSW was sex with a woman. A greater percentage of MSW and women reported they likely acquired HIV from injection drug use (IDU), another non-sexual route, or an unknown route, compared to MSM. Most MSM were white, and only 1% were of black African ethnicity. In contrast, the most common ethnic group among MSW and women was black African. The median age of women was lower than for either of the male groups.

MSW and women had poorer SES than MSM by all four markers: a much higher percentage reported being less able to afford basic needs, being unemployed, renting housing from the council or being in temporary housing or homeless. A higher proportion of MSW and women (compared to MSM) reported having no formal education or education below university level, although these differences in education were somewhat smaller than the differences by the other SES markers. In general, when comparing MSW with women, levels of socio-economic disadvantage tended to be somewhat poorer among women.

Most MSW or women were born in a country other than the UK, with the majority born in an African country, whereas UK-birth was most common for MSM. The proportion of individuals living in the UK for fewer than five years was small for each group, but highest among women. Not being able to read English fluently was much more

common for MSW and women compared to MSM. Levels of reported supportive network were similar between the gender/sexual orientation groups, however, MSW were more likely to have a current partner compared to the other two groups.

Prevalence of symptoms of major depression was similar between gender/sexual orientation groups; however, a greater percentage of women had depression symptoms under the “major or other depression” definition. MSM were much more likely to have used recreational drugs in the last three months, and both male groups were more likely to have evidence of alcohol dependency compared to women.

MSM were more likely to have been diagnosed with HIV longer compared to MSW and women, and they had a greater median number of years on ART. The proportion taking once-a-day regimens was similar between the gender/sexual orientation groups.

A greater percentage of MSW and women self-reported ≥2 consecutive missed days of ART in the past three months, compared to MSM. On the other hand similar percentages of MSM and MSW self-reported ≥1 missed dose in the last two weeks, compared to a higher proportion among women.

Table 8.1: Characteristics of questionnaire respondents included in cross-sectional ART non-adherence analysis by gender/sexual orientation [a]

Factor		MSM		MSW		Women		P-value[b]
		N	% [c]	N	% [c]	N	% [c]	
Total		**1867**	**69%**	**321**	**12%**	**516**	**19%**	
Likely mode of HIV acquisition	Sex with a man	1742	93%	6	2%	347	67%	<.0001
	Sex with a woman	8	<1%	189	59%	0	0%	
	IDU	13	1%	18	6%	15	3%	
	Unknown	76	4%	74	23%	103	20%	
	Other	23	1%	33	10%	44	9%	
	Missing	5	<1%	1	<1%	7	1%	
Ethnicity	White	1665	89%	103	32%	107	21%	<.0001
	Black African	14	1%	163	51%	330	64%	
	Black Other	36	2%	21	7%	32	6%	
	Other	125	7%	27	8%	32	6%	
	Missing	27	1%	7	2%	15	3%	
Age	Median (IQR [d])	46 (40, 52)		47 (42, 53)		43 (37, 49)		<.0001
Afford basic needs (financial hardship)	Always	968	52%	89	28%	113	22%	<.0001
	Mostly	502	27%	74	23%	125	24%	
	Sometimes	230	12%	91	28%	143	28%	
	No	147	8%	58	18%	121	23%	
	Missing	20	1%	9	3%	14	3%	
Employment	Employed	1101	59%	144	45%	234	45%	<.0001
	Unemployed	265	14%	85	26%	133	26%	
	Sick/ disabled	286	15%	34	11%	55	11%	
	Retired	142	8%	24	7%	14	3%	
	Other	44	2%	23	7%	60	12%	
	Missing	29	2%	11	3%	20	4%	
Housing	Homeowner	799	43%	68	21%	77	15%	<.0001
	Renting from council	511	27%	113	35%	216	42%	
	Renting privately	406	22%	75	23%	128	25%	
	Temporary/homeless	18	1%	22	7%	30	6%	
	Staying with family/other	113	6%	35	11%	53	11%	
	Missing	20	1%	8	2%	12	2%	
Education (highest level)	University degree or higher	811	43%	117	36%	166	32%	<.0001
	A-level/equivalent	379	20%	55	17%	102	20%	
	O-levels/equivalent	420	23%	77	24%	104	20%	
	Other	50	3%	14	4%	44	9%	
	None	183	10%	47	15%	72	14%	
	Missing	24	1%	11	3%	28	5%	
Country of birth [e]	UK	1329	71%	86	27%	96	19%	<.0001
	Europe (non-UK)	216	12%	22	7%	23	4%	
	Africa	71	4%	171	53%	324	63%	
	North America	53	3%	6	2%	5	1%	
	South America	65	3%	6	2%	6	1%	
	Asia	42	2%	5	2%	3	1%	
	Australia	30	2%	0	0%	1	<1%	
	Unknown (non-UK)	40	2%	17	5%	37	7%	
	Missing	21	1%	8	2%	21	4%	
Time in UK	Born in UK	1329	71%	86	27%	96	19%	<.0001
	>5 years	440	24%	206	64%	345	67%	
	≤5 years	62	3%	16	5%	38	7%	
	Missing	36	2%	13	4%	37	7%	
English reading ability	Born in UK	1329	71%	86	27%	96	19%	<.0001
	Fluent	454	24%	162	50%	296	57%	
	Not fluent	54	3%	61	19%	93	18%	

Factor		MSM		MSW		Women		P-value[b]
		N	% [c]	N	% [c]	N	% [c]	
Total		**1867**	**69%**	**321**	**12%**	**516**	**19%**	
	Missing	30	2%	12	4%	31	6%	
Supportive network	Most support	600	32%	118	37%	160	31%	0.16
	Medium support	1001	54%	153	48%	260	50%	
	Least support	259	14%	37	12%	81	16%	
	Missing	7	<1%	13	4%	15	3%	
Children	Yes	133	7%	220	69%	380	74%	<.0001
	No	1725	92%	99	31%	130	25%	
	Missing	9	<1%	2	1%	6	1%	
Partner	Yes	1030	55%	223	69%	277	54%	<.0001
	No	825	44%	97	30%	236	46%	
	Missing	12	1%	1	<1%	3	1%	
Major depressive symptoms	Yes	342	18%	60	19%	104	20%	0.64
	No	1525	82%	261	81%	412	80%	
Major or other depressive symptoms	Yes	469	25%	90	28%	166	32%	0.0052
	No	1398	75%	231	72%	350	68%	
Reported recreational drug use in past 3 months	Yes	932	49%	50	15%	35	7%	<.0001
	No	935	51%	271	85%	481	93%	
Alcohol dependency problem	Yes	349	19%	57	18%	58	11%	0.0005
	No	1518	81%	262	82%	453	88%	
	Missing	0	0%	2	1%	5	1%	
Time since HIV diagnosis	<2 years	101	5%	35	11%	44	9%	<.0001
	2-5 years	234	13%	52	16%	75	15%	
	5-15 years	897	48%	157	49%	291	56%	
	>15 years	596	32%	63	20%	96	19%	
	Missing	39	2%	14	4%	10	2%	
Number of times taking ART per day	1	1485	80%	259	81%	415	80%	0.34
	≥2	370	20%	55	17%	88	17%	
	Missing	12	1%	7	2%	13	3%	
SR ≥2 consecutive missed days of ART in past 3 months	No/don't know	1575	84%	262	80%	399	77%	0.0006
	Yes	289	15%	58	18%	117	23%	
	Missing	3	<1%	1	<1%	0	0%	
SR ≥1 missed dose in the last 2 weeks	No/don't know	1412	76%	239	74%	371	72%	0.27
	Yes	455	24%	78	24%	143	28%	
	Missing	0	0%	4	1%	2	<1%	
Non-adherent to ART [f]	No/don't know	1298	70%	217	68%	316	61%	0.0018
	Yes	569	30%	104	32%	200	39%	
Time on ART (years) [g h]	Median (IQR [d])	7.6 (3.2, 13.3)		6.6 (2.5, 10.8)		6.5 (2.6, 10.7)		<.0001
CD4 count [i] (cells/μL)	Median (IQR [d])	560 (420, 740)		447 (300, 664)		540 (379, 740)		<.0001
VL at the time of the questionnaire	≤50 copies/mL	1648	88%	261	81%	438	85%	0.0009
	>50 copies/mL	208	11%	58	18%	75	15%	
	Missing	11	1%	2	1%	3	1%	

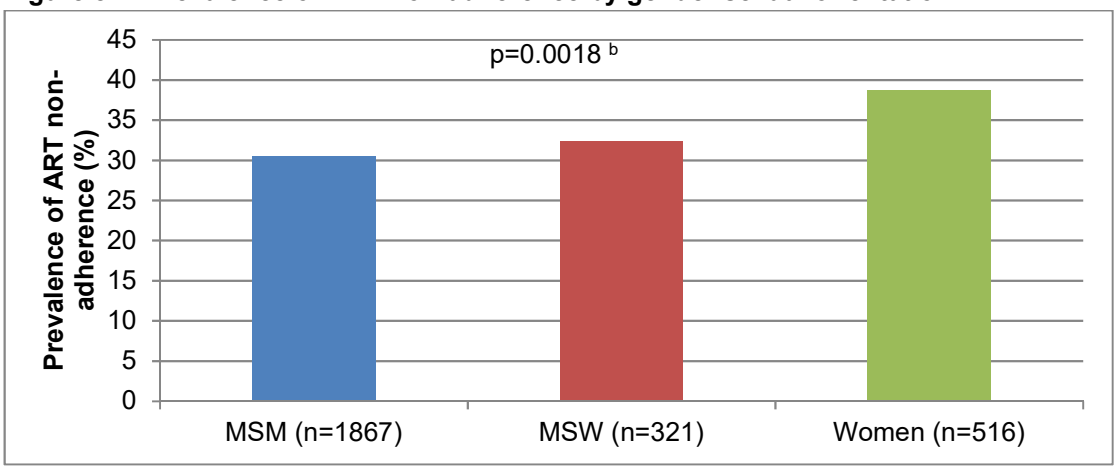
[a] 2704 participants included who self-reported being on ART at the time of the questionnaire and had recorded age and non-adherence data; [b] some column percentages do not sum to 100% due to rounding; [c] Chi-squared test for categorical and Wilcoxon-Mann-Whitney test for continuous variables, after missing values excluded; [d] IQR= interquartile range; [e] grouped by continent except for UK; [f] self-reported ART non-adherence: ≥2 consecutive missed days of ART in the past 3 months or ≥1 missed dose in the last 2 weeks; [g] missing time on ART: MSM=65 (3%), MSW=16 (5%), women=18 (3%); [h] among those with known date started ART; [i] missing CD4 count: MSM=10 (1%), MSW=4 (1%), women=3 (1%); SR= self-reported.

8.4.2 Cross-sectional self-reported ART non-adherence

8.4.2.1 *The association between gender/sexual orientation and ART non-adherence*

As noted above, there were differences according to gender/sexual orientation in the prevalence of ART non-adherence. Using my definition, among the 2704 individuals eligible for the non-adherence analysis, 569/1867 (31%) MSM, 104/321 (32%) MSW, and 200/516 (39%) women self-reported ART non-adherence at the time of the questionnaire (p=0.0018). This is displayed in Figure 8.1.

Figure 8.1: Prevalence of ART non-adherence by gender/sexual orientation [a]



[a] Cross-sectional analysis among 2704 respondents who self-reported being on ART at the time of the questionnaire, self-reported ART non-adherence: ≥2 consecutive missed days of ART in the past 3 months or ≥1 missed dose in the last 2 weeks; [b] Chi square test.

8.4.2.2 *The association between the other covariates and ART non-adherence*

The associations of socio-economic factors with ART non-adherence have previously been displayed in Section 7.4.2 and Table 7.2. Poorer SES by any of the four markers considered was found to be associated with a greater prevalence of ART non-adherence.

In addition, younger age, African country of birth, not being UK-born but living in the UK for over five years, having non-fluent English reading ability, not having a current partner, major or other depressive symptoms, recreational drug use in the last three months, and evidence of alcohol dependency were all strongly associated with greater prevalence of ART non-adherence (Table 8.2).

Table 8.2: Prevalence of ART non-adherence [a] by demographic, social circumstance, mental health and lifestyle factors

Factor [b]		Frequency (%)		P-value[c]
Demographic factors				
Age	<30 years	41/103	39.8%	<0.0001 [d]
	30-49 years	613/1767	34.7%	
	≥50 years	219/834	26.3%	
Social circumstance factors				
Country of birth	Born in UK	443/1511	29.3%	<0.0001
	Non-UK: European	79/261	30.3%	
	Non-UK: African	230/566	40.6%	
	Non-UK: other/unknown	99/316	31.3%	
Time in the UK	Born in UK	443/1511	29.3%	0.0008
	>5 years	361/991	36.4%	
	≤5 years	34/116	29.3%	
English reading ability	Born in UK	443/1511	29.3%	<0.0001
	Fluent	303/912	33.2%	
	Non-fluent	97/208	46.6%	
Supportive network	Most support	218/878	24.8%	<0.0001 [d]
	Medium support	489/1414	34.6%	
	Least support	153/377	40.6%	
Current partner	Yes	459/1530	30.0%	0.0035
	No	409/1158	35.3%	
Mental health factors				
Major Depression	Yes	220/506	43.5%	<0.0001
	No	653/2198	29.7%	
Major or other depression	Yes	305/725	42.1%	<0.0001
	No	568/1979	28.7%	
Lifestyle factors				
Recreational drug use	Yes	392/1017	38.5%	<0.0001
	No	481/1687	28.5%	
Alcohol dependency	Yes	190/464	41.0%	<0.0001
	No	678/2233	30.4%	

[a] Self-reported ART non-adherence: ≥1 missed dose in the past 3 months for ≥2 consecutive days or ≥1 missed dose in the last 2 weeks; [b] individuals with missing values for explanatory variables were excluded; [c] Chi square test; [d] Cochran-Armitage test for trend.

8.4.2.3 *Gender/sexual orientation and ART non-adherence: effect of adjustment for other covariates*

Table 8.3 shows the results from a number of modified Poisson regression models assessing the association of gender/sexual orientation with ART non-adherence using PRs. The first model was unadjusted, followed by models were adjusted sequentially for factors as described in Section 8.3.5.1 . In the unadjusted analysis, there was no evidence of a difference in ART non-adherence between the male groups, as the PR was close to one (1.06, p=0.49 for MSW vs. MSM). In contrast, women had a 27% and 20% increased prevalence of ART non-adherence compared to MSM and MSW, respectively. Adjustment for age attenuated these associations by 5% and 7% (in relative terms), respectively, thus although the difference in non-adherence between women and MSW was partially explained by age differences, there remained evidence of greater non-adherence among women, even after accounting for age (Table 8.3).

Since there was little difference in the prevalence of ART non-adherence observed between MSW and MSM in unadjusted analyses or analyses adjusted for age only, additional adjustment for any of the SES factors had little effect. In contrast, additional adjustment for any one of financial hardship, employment, or housing status, and to a lesser extent education, attenuated the PRs for women vs. MSM toward one. Using stepwise selection, financial hardship and housing status were chosen as the two most significant predictors, among SES factors, of ART non-adherence. As adjustment for financial hardship alone completely attenuated the differences between MSM and women, adjusting for this subset of two socio-economic factors, or for all four socio-economic factors together was unable to attenuate the differences any further. With regard to the differences between women and MSW, adjustment for any single SES factor or multiple SES factors had little effect on attenuating the PRs for women vs. MSW over and above age.

When considering social circumstance, lifestyle and mental health factors, adjustment for most of these factors made only minor differences to the age adjusted PRs for each pairwise comparison. Country of birth, time in the UK and English reading ability attenuated each of the pairwise differences to the greatest extent. In particular, adjustment for country of birth attenuated the differences in adherence between MSM and women substantially, perhaps indicating that differences were also related to migrant status. Recreational drug use accentuated the difference in prevalence of ART non-adherence between MSW and MSM and between women and MSM because recreational drug use was associated with non-adherence and the prevalence of drug use was substantially greater among MSM.

Table 8.3: Cross-sectional association between gender/sexual orientation and ART non-adherence [a] following adjustment for SES, social circumstance, mental health, and lifestyle factors in separate models (N=2704)

Adjusted for [b]:	PR (95% CI)						P-value[c]
	MSW vs. MSM		Women vs. MSM		Women vs. MSW		
Unadjusted	1.06	0.89, 1.26	1.27	1.11, 1.45	1.20	0.99, 1.45	0.0027
Age	1.08	0.91, 1.29	1.21	1.06, 1.38	1.12	0.92, 1.35	0.019
SES factors							
Adjusted for age and:							
Financial hardship	0.92	0.77, 1.10	1.01	0.88, 1.16	1.10	0.91, 1.34	0.58
Employment	1.03	0.87, 1.23	1.13	0.99, 1.30	1.10	0.90, 1.34	0.22
Housing status	1.00	0.84, 1.19	1.10	0.97, 1.26	1.11	0.91, 1.34	0.35
Education	1.09	0.91, 1.29	1.17	1.02, 1.33	1.07	0.88, 1.31	0.084
Multiple SES factors							
Adjusted for age and:							
All SES factors [d]	0.90	0.75, 1.08	0.97	0.85, 1.12	1.08	0.89, 1.32	0.48
Stepwise selected subset of SES factors [e]	0.90	0.75, 1.07	0.99	0.86, 1.13	1.10	0.91, 1.34	0.45
Social circumstance factors							
Adjusted for age and:							
Country of birth	0.90	0.74, 1.10	0.97	0.81, 1.16	1.07	0.88, 1.30	0.60
Time in the UK	1.03	0.86, 1.24	1.11	0.96, 1.29	1.07	0.88, 1.31	0.39
English reading ability	0.99	0.82, 1.18	1.07	0.93, 1.25	1.09	0.89, 1.33	0.58
Supportive network	1.11	0.94, 1.33	1.20	1.06, 1.37	1.08	0.89, 1.31	0.022
Current stable partner	1.12	0.94, 1.33	1.21	1.06, 1.38	1.08	0.89, 1.31	0.016
Mental health factors							
Adjusted for age and:							
Major depression	1.08	0.91, 1.28	1.21	1.06, 1.37	1.11	0.92, 1.35	0.022
Major or other depression	1.07	0.90, 1.27	1.18	1.04, 1.34	1.10	0.91, 1.33	0.048
Lifestyle factors							
Adjusted for age and:							
Recreational drug use	1.26	1.06, 1.51	1.50	1.30, 1.73	1.19	0.98, 1.44	<.0001
Alcohol dependency	1.08	0.91, 1.29	1.23	1.08, 1.40	1.14	0.94, 1.38	0.011

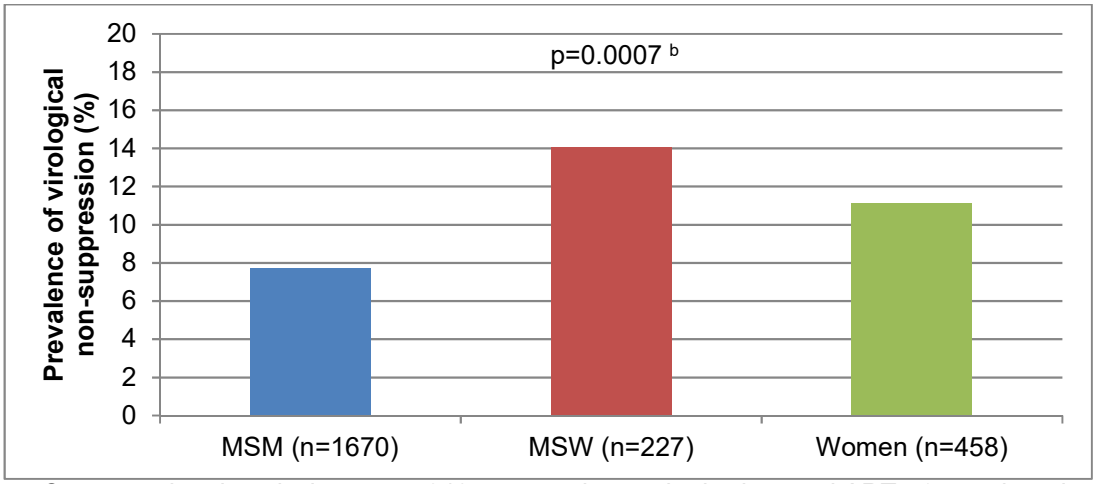
[a] Self-reported ART non-adherence: ≥1 missed dose in the past 3 months for ≥2 consecutive days or ≥1 missed dose in the last 2 weeks; [b] individuals with missing values for explanatory variables were excluded; [c] Chi square test; [d] financial hardship, employment, housing status, and education; [e] financial hardship and housing status only. PR = Prevalence Ratio; SES = socio-economic status.

8.4.3 Cross-sectional virological non-suppression

8.4.3.1 *The association between gender/sexual orientation and virological non-suppression*

Among the 2405 individuals included in the analysis, virological non-suppression (>50 copies/mL) was more prevalent among MSW and women compared to MSM (14% [39/277] and 11% [51/458] vs. 8% [129/1670] respectively, p=0.0007) shown in Figure 8.2.

Figure 8.2: Prevalence of virological non-suppression by gender/sexual orientation [a]



[a] Cross-sectional analysis among 2405 respondents who had started ART >6 months prior to completion of the questionnaire; [b] Chi square test.

8.4.3.2 *The association between the other covariates and virological non-suppression*

The associations of the SES factors with VL non-suppression among people on ART were previously shown in Section 7.4.3 and Table 7.3. Lower SES by any marker was associated with a higher prevalence of virological non-suppression.

The association of demographic, social circumstance, mental health and lifestyle factors with virological non-suppression are shown in Table 8.4. Younger age, being born in Africa, non-fluent English reading ability, depression and alcohol dependency were each associated with a higher prevalence of virological non-suppression. There was also weak evidence that living in the UK for over five years but not being UK-born, least supportive network, and not having a current partner were associated with a higher prevalence of virological non-suppression. In contrast, there was no evidence that recreational drug use was associated with this outcome.

Table 8.4: Prevalence of virological non-suppression [a] by demographic, social circumstance, mental health and lifestyle factors

Factor [b]		Frequency (%)		P-value[c]
Demographic factors				
Age	<30 years	12/73	16.4%	0.0033 [d]
	30-49 years	153/1563	9.8%	
	≥50 years	54/769	7.0%	
Social circumstance factors				
Country of birth	Born in UK	108/1329	8.1%	0.035
	Non-UK: European	16/235	6.8%	
	Non-UK: African	62/513	12.1%	
	Non-UK: other/unknown	25/282	8.9%	
Time in the UK	Born in UK	108/1329	8.1%	0.085
	>5 years	95/899	10.6%	
	≤5 years	6/98	6.1%	
English reading ability	Born in UK	108/1329	8.1%	0.0056
	Fluent	73/825	8.9%	
	Non-fluent	28/182	15.4%	
Supportive network	Most support	63/762	8.3%	0.059 [d]
	Medium support	113/1273	8.9%	
	Least support	42/342	12.3%	
Current partner	Yes	112/1363	8.2%	0.090
	No	105/1026	10.2%	
Mental health factors				
Major Depression	Yes	67/456	14.7%	<0.0001
	No	152/1949	7.8%	
Major or other depression	Yes	93/652	14.3%	<0.0001
	No	126/1753	7.2%	
Lifestyle factors				
Recreational drug use	Yes	78/899	8.7%	0.57
	No	141/1506	9.4%	
Alcohol dependency	Yes	55/421	13.1%	0.0020
	No	164/1979	8.3%	

[a] VL >50 copies/mL; [b] individuals with missing values for explanatory variables were excluded; [c] Chi square test; [d] Cochran-Armitage test for trend.

8.4.3.3 *Gender/sexual orientation and virological non-suppression: effect of adjustment for other covariates*

Table 8.5 shows the unadjusted association between gender/sexual orientation and virological non-suppression, and the association following adjustment for SES and other factors. In unadjusted analyses, MSW and women had 82% and 44% greater prevalence of virological non-suppression compared to MSM, respectively, and there was weak evidence of 21% lower prevalence among women compared to MSW. Adjustment for age alone did not substantially alter the difference in prevalence between MSW and MSM. However, it attenuated the PR between women and MSM to some extent, such that there was only weak evidence of a difference in virological non-suppression between these groups after controlling for age. Adjustment for age actually accentuated the differences between women and MSW, such that women had 31% lower prevalence of virological non-suppression compared to MSW.

When considering MSW compared to MSM, while the difference in prevalence of virological non-suppression was attenuated to some extent by adjustment for any of the socio-economic factors, there remained a substantial difference between MSW and MSM. Adjustment for all SES factors or the stepwise selected subset of SES factors (in this case housing status and employment), attenuated the PR towards one, further than any single factor. However, the PR was still substantial at 1.43, suggesting a substantially higher prevalence of virological non-suppression for MSW compared to MSM, even when SES was accounted for. Similarly, for women versus MSM, additional adjustment for any socio-economic factor attenuated the PR for the difference between women and MSM further towards one. In particular, following adjustment for age and financial hardship there was no evidence of a difference between these groups (PR=0.99). Thus, additional adjustment multiple socio-economic factors was unable to attenuate the differences any further. Finally, when comparing women to MSW, adjustment for age and financial hardship, employment, education or multiple SES factors together actually increased the effect size for the difference in virological non-suppression. This was likely because in this study women tended to have poorer SES than MSW. Thus, higher prevalence of virological non-suppression in MSW compared to women could possibly be even larger than those found in analyses unadjusted for SES.

For both MSW versus MSM and women versus MSM, adjustment for country of birth and English reading ability made the most substantial attenuations to PRs of the social circumstance, mental health, and lifestyle factors - to the extent that the PRs were similar to the models which adjusted for a single SES factor. Adjustment for any of the other factors made little difference to the PRs. None of the social circumstances, mental health, or lifestyle factors had a considerable effect on the differences in virological non-suppression between women and MSW above that of age.

Table 8.5: Cross-sectional association between gender/sexual orientation and virological non-suppression [a] following adjustment for SES, social circumstance, mental health, and lifestyle factors in separate models (N=2405)

Adjusted for [b]:	PR (95% CI)						P-value[c]
	MSW vs. MSM		Women vs. MSM		Women vs. MSW		
Unadjusted	1.82	1.30, 2.55	1.44	1.06, 1.96	0.79	0.54, 1.17	0.0033
Age	1.88	1.35, 2.63	1.30	0.95, 1.76	0.69	0.47, 1.02	0.0053
SES factors							
Adjusted for age and:							
Financial hardship	1.50	1.05, 2.14	0.99	0.71, 1.37	0.66	0.44, 0.98	0.12
Employment	1.63	1.15, 2.31	1.07	0.77, 1.48	0.65	0.43, 0.98	0.063
Housing status	1.50	1.06, 2.12	1.05	0.76, 1.43	0.70	0.47, 1.04	0.13
Education	1.83	1.30, 2.58	1.19	0.86, 1.63	0.65	0.43, 0.97	0.015
Multiple SES factors							
Adjusted for age and:							
All SES factors [d]	1.39	0.96, 2.01	0.90	0.64, 1.25	0.64	0.43, 0.97	0.14
Stepwise selected subset of SES factors [e]	1.43	1.00, 2.04	0.96	0.70, 1.33	0.67	0.45, 1.01	0.17
Social circumstance factors							
Adjusted for age and:							
Country of birth	1.66	1.14, 2.42	1.14	0.77, 1.68	0.69	0.45, 1.04	0.067
Time in the UK	1.79	1.25, 2.56	1.23	0.87, 1.72	0.68	0.45, 1.03	0.021
English reading ability	1.70	1.17, 2.49	1.21	0.86, 1.71	0.71	0.47, 1.08	0.051
Supportive network	1.93	1.38, 2.69	1.31	0.96, 1.77	0.68	0.46, 1.00	0.0042
Current stable partner	2.01	1.44, 2.82	1.32	0.97, 1.79	0.65	0.44, 0.97	0.0023
Mental health factors							
Adjusted for age and:							
Major depression	1.88	1.35, 2.62	1.28	0.94, 1.74	0.68	0.46, 1.01	0.0059
Major or other depression	1.84	1.32, 2.56	1.23	0.90, 1.66	0.67	0.45, 0.98	0.0095
Lifestyle factors							
Adjusted for age and:							
Recreational drug use	1.91	1.34, 2.71	1.32	0.94, 1.85	0.69	0.47, 1.02	0.0075
Alcohol dependency	1.91	1.37, 2.66	1.36	1.00, 1.85	0.71	0.48, 1.05	0.0031

[a] VL >50 copies/mL; [b] individuals with missing values for explanatory variables were excluded; [c] Chi square test; [d] financial hardship, employment, housing status, and education; [e] employment and housing status only. PR = Prevalence Ratio; SES = socio-economic status.

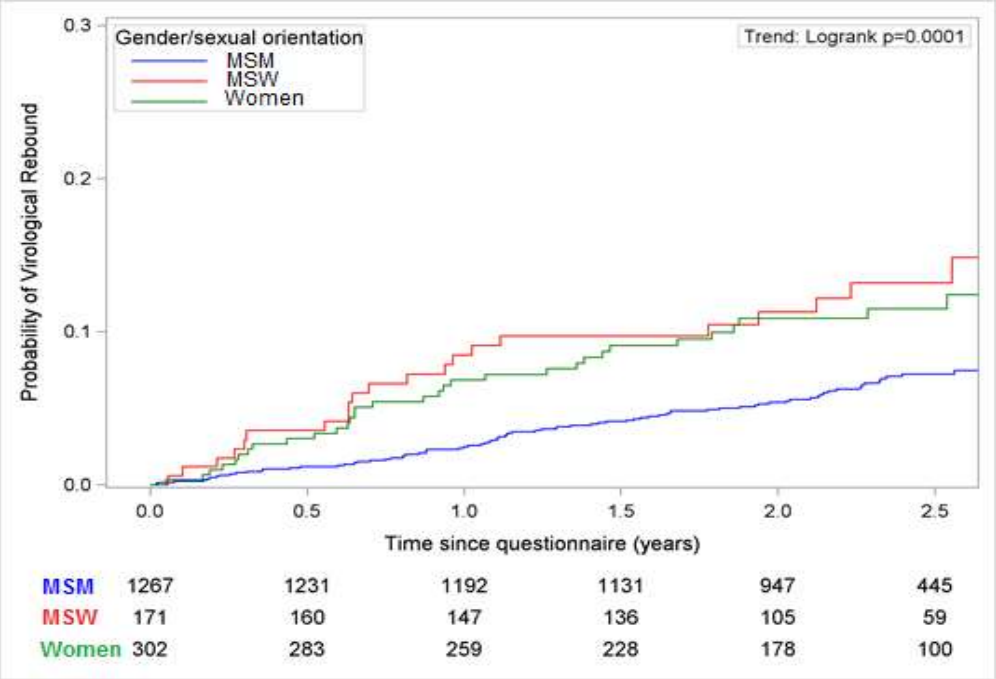
8.4.4 **Longitudinal virological rebound**

8.4.4.1 ***The association between gender/sexual orientation and virological rebound***

Of the 1740 ASTRA participants included in the longitudinal analyses, 82 (6%) MSM, 22 (13%) MSW, and 35 (12%) women experienced virological rebound (p=0.0006; log rank test), over 2851, 350, and 617 person-years, respectively. The median number of years of follow-up (median [IQR]: MSM: 2.4 [2.1, 2.7]; MSM: 2.3 [1.9, 2.7]; women: 2.3 [1.7, 2.7]) and number of VL measurements (MSM: 6 [5, 8]; MSW: 6 [4, 8]; women: 5 [4, 7]) were similar for the gender/sexual orientation groups.

At 1 year MSM, MSW and women had a Kaplan Meier probability of rebound (95% CI) of 2.6% (1.7%, 3.4%), 9.1% (4.7%, 13.5%) and 7.2% (4.2%, 10.2%), respectively, and at 2 years this was 5.5% (4.2%, 6.8%), 12.2% (7.0%, 17.4%), and 11.5% (7.6%, 15.4%), respectively (Figure 8.3).

Figure 8.3: Kaplan-Meier plot of time until virological rebound according to gender/sexual orientation [a] (N=1740)



[a] VL ≤50copies/mL at the time of the questionnaire and one subsequent VL >200copies/mL.

8.4.4.2 *The association between the other covariates and virological rebound*

The rates of virological rebound in the different socio-economic groups are provided in Section 7.4.5 and Table 7.5. Higher rates of virological rebound were found among those with poorer SES by each of the four markers.

Additionally, higher rates of virological rebound were found among younger individuals, individuals born in African countries, individuals without a current partner, and individuals with major or other depressive symptoms (Table 8.6). In contrast, virological rebound was not associated with time in the UK, English reading ability, supportive network, recreational drug use, and alcohol dependency.

Table 8.6: Rate of virological rebound [a] by mental health and lifestyle factors

Factor [b]		Rate	95% CI	P-value[c]
Demographic factors				
Age	<30 years	8.74	6.24, 11.24	0.0028 [d]
	30-49 years	4.06	3.82, 4.30	
	≥50 years	2.51	2.31, 2.72	
Social circumstance factors				
Country of birth	Born in UK	3.09	2.36, 3.82	0.0043
	Non-UK: European	3.17	1.38, 4.96	
	Non-UK: African	6.17	4.30, 8.04	
	Non-UK: other/unknown	2.84	1.30, 4.38	
Time in the UK	Born in UK	3.09	2.36, 3.82	0.17
	>5 years	4.47	4.12, 4.82	
	≤5 years	2.96	2.26, 3.66	
English reading ability	Born in UK	3.09	2.36, 3.82	0.27
	Fluent	4.35	4.00, 4.70	
	Non-fluent	4.43	3.61, 5.24	
Supportive network	Most support	3.07	2.82, 3.33	0.078 [d]
	Medium support	3.68	3.45, 3.92	
	Least support	5.04	4.38, 5.69	
Current partner	Yes	2.96	2.77, 3.14	0.0065
	No	4.65	4.31, 4.99	
Mental health factors				
Major Depression	Yes	8.13	5.90, 10.36	<0.0001
	No	2.76	2.19, 3.33	
Major or other depression	Yes	6.96	5.23, 8.69	<0.0001
	No	2.63	2.04, 3.22	
Lifestyle factors				
Recreational drug use	Yes	4.10	3.09, 5.11	0.16
	No	3.33	2.58, 4.08	
Alcohol dependency	Yes	4.54	2.89, 6.19	0.18
	No	3.44	2.79, 4.09	

[a] VL≤50 copies/mL at the time of the questionnaire and one subsequent VL>200 copies/mL; [b] individuals with missing values for explanatory variables were excluded; [c] Chi square test.

8.4.4.3 *Gender/sexual orientation and virological rebound: effect of adjustment for other covariates*

Table 8.7 shows the HRs for the association between gender/sexual orientation and virological rebound from a Cox regression model. In an unadjusted analysis, MSW and women had 2.2 and 2.0 times the hazard rate of virological rebound compared to MSM, respectively. However, there was no difference between MSW and women, with a HR close to 1.00 (p=0.69 for MSW vs. women). Adjustment for age attenuated the HR comparing virological rebound between women and MSM somewhat. However, it actually led to a greater difference in the rate of rebound between MSW and MSM and between women and MSW; likely the result of the younger median age among women compared to both male groups.

Additional adjustment for any of financial hardship, employment status, housing status, stepwise selected subset of SES factors (in this case employment and housing), or all four SES factors explained some of the differences in rate of virological rebound

between MSW and MSM. However, there remained substantial differences between the two groups of men even after adjustment for multiple SES factors. These were also the factors that most attenuated the differences between women and MSM, although there was some evidence that a difference between these groups remained. For women versus MSW, adjustment for employment in addition to age accentuated the HR for virological rebound further, though there was still not a statistically significant difference between these groups. Adjustment education made little difference to the HR.

Adjustment for country of birth attenuated the differences in virological rebound between MSW and MSM and between women and MSM to a similar extent as when adjusted for one of the SES factors. Adjustment for depressive symptoms somewhat attenuated the PRs for MSW versus MSM and women versus MSM, but to a lesser extent than the markers of current SES. On the other hand, adjustment for major depression accentuated the PR for differences between women and MSW, such that women had 0.6 times the rate of virological rebound compared to MSW. Alcohol dependence was unable to attenuate differences in virological rebound between MSW and MSM or between women and MSM; however, adjustment for recreational drug use accentuated differences between these groups. There was little evidence of a difference between women and MSW when adjusted for age and any one lifestyle factor.

Table 8.7: Longitudinal association between gender/sexual orientation and virological rebound following adjustment for SES, social circumstance, mental health, and lifestyle factors in separate models [a] (N=1740)

Adjusted for [b]:	HR (95% CI)						P-value[c]
	MSW vs. MSM		Women vs. MSM		Women vs. MSW		
Unadjusted	2.18	1.36, 3.49	1.96	1.32, 2.91	0.90	0.53, 1.53	0.0002
Age	2.34	1.46, 3.76	1.79	1.20, 2.66	0.76	0.44, 1.31	0.0002
SES factors							
Adjusted for age and:							
Financial hardship	1.98	1.21, 3.22	1.44	0.94, 2.19	0.73	0.42, 1.26	0.015
Employment	2.09	1.30, 3.37	1.39	0.92, 2.11	0.67	0.38, 1.15	0.0065
Housing status	1.98	1.22, 3.20	1.49	0.99, 2.24	0.75	0.43, 1.30	0.0095
Education	2.32	1.43, 3.77	1.65	1.09, 2.50	0.71	0.41, 1.25	0.0007
Multiple SES factors							
Adjusted for age and:							
All SES factors [d]	1.68	1.02, 2.77	1.32	0.86, 2.04	0.80	0.45, 1.37	0.10
Stepwise selected subset of SES factors [e]	1.73	1.07, 2.80	1.44	0.95, 2.16	0.83	0.48, 1.42	0.042
Social circumstance factors							
Adjusted for age and:							
Country of birth	2.01	1.16, 3.47	1.37	0.81, 2.31	0.68	0.39, 1.19	0.044
Time in the UK	2.28	1.37, 3.81	1.64	1.04, 2.60	0.72	0.41, 1.27	0.0034
English reading ability	2.48	1.49, 4.12	1.66	1.05, 2.62	0.67	0.38, 1.17	0.0012
Supportive network	2.49	1.55, 4.01	1.78	1.19, 2.67	0.72	0.41, 1.24	0.0001
Current stable partner	2.53	1.57, 4.08	1.83	1.23, 2.72	0.72	0.42, 1.24	0.0011
Mental health factors							
Adjusted for age and:							
Major depression	2.21	1.38, 3.55	1.71	1.15, 2.56	0.55	0.45, 1.33	0.0007
Major or other depression	2.24	1.39, 3.59	1.69	1.13, 2.52	0.75	0.44, 1.30	0.0007
Lifestyle factors							
Adjusted for age and:							
Recreational drug use	2.78	1.70, 4.55	2.30	1.47, 3.61	0.83	0.48, 1.43	<.0001
Alcohol dependency	2.30	1.42, 3.73	1.86	1.25, 2.79	0.81	0.47, 1.41	0.0002

[a] VL ≤50 copies/mL at the time of the questionnaire and one subsequent VL >200 copies/mL; [b] individuals with missing values for explanatory variables were excluded; [c] Chi square test; [d] financial hardship, employment, housing status, and education; [e] employment and housing status only. HR = Hazard Ratio; SES = socio-economic status.

8.4.5 **Sensitivity analyses**

8.4.5.1 ***Virological non-suppression sensitivity analysis***

Virological non-suppression was redefined as a VL >200 copies/mL at the time of the questionnaire instead of >50 copies/mL as in the main analysis. As expected the prevalence of virological non-suppression was even lower: of the 2405 individuals included, 68/1670 (4%) MSM had a VL >200 copies/mL, compared to 25/277 (9%) MSW and 22/458 (5%) women (p=0.0017).

The PRs for the association of gender/sexual orientation and VL >200 copies/mL are displayed in Table 8.8. Using this definition, there was still a large difference in the prevalence of virological non-suppression in favour of MSM versus MSW, which was, if anything, larger in magnitude compared to that seen when using a 50 copies/ml VL cut-off. However, there was little evidence of a difference between women and MSM. In addition, women had half the prevalence of virological non-suppression compared to MSW under this definition.

Adjustment for age accentuated the differences between the groups observed in unadjusted analyses. Additional adjustment for financial hardship, employment, housing status, or multiple SES factors attenuated the differences between MSW and MSM to some extent. There remained no evidence of a statistically significant difference in the prevalence of virological non-suppression between women and MSM following adjustment for any of the SES, social circumstances, mental health, or lifestyle factors. There was also no evidence that any of these factors explained the differences in virological non-suppression between women and MSW; this was as expected since women generally have poorer SES than MSW.

Table 8.8: Sensitivity analysis: virological non-suppression defined as VL >200 copies/mL (N=2405)

Adjusted for [b]:	PR (95% CI)						P-value[c]
	MSW vs. MSM		Women vs. MSM		Women vs. MSW		
Unadjusted	2.22	1.43, 3.44	1.18	0.74, 1.89	0.53	0.31, 0.93	0.022
Age	2.31	1.49, 3.59	1.03	0.64, 1.66	0.45	0.25, 0.78	0.017
SES factors							
Adjusted for age and:							
Financial hardship	1.77	1.10, 2.86	0.73	0.44, 1.20	0.41	0.23, 0.72	0.018
Employment	2.00	1.26, 3.16	0.77	0.46, 1.30	0.39	0.21, 0.70	0.017
Housing status	1.92	1.22, 3.02	0.83	0.51, 1.35	0.43	0.25, 0.76	0.030
Education	2.31	1.49, 3.59	0.97	0.60, 1.56	0.42	0.24, 0.74	0.016
Multiple SES factors							
Adjusted for age and:							
All SES factors [d]	1.70	1.03, 2.80	0.65	0.39, 1.09	0.38	0.22, 0.69	0.0088
Stepwise selected subset of SES factors [e]	1.81	1.13, 2.90	0.71	0.42, 1.19	0.39	0.22, 0.70	0.016
Social circumstance factors							
Adjusted for age and:							
Country of birth	2.23	1.35, 3.68	0.99	0.55, 1.77	0.44	0.25, 0.79	0.024
English reading ability	2.36	1.43, 3.90	1.08	0.65, 1.81	0.46	0.25, 0.83	0.029
Supportive network	2.43	1.57, 3.76	1.03	0.64, 1.65	0.42	0.24, 0.74	0.012
Current stable partner	2.61	1.69, 4.05	1.05	0.66, 1.69	0.40	0.23, 0.71	0.0076
Mental health factors							
Adjusted for age and:							
Major depression	2.29	1.48, 3.55	1.01	0.63, 1.63	0.44	0.25, 0.77	0.017
Major or other depression	2.22	1.43, 3.42	0.94	0.58, 1.51	0.42)	0.24, 0.74	0.017
Lifestyle factors							
Adjusted for age and:							
Recreational drug use	2.38	1.48, 3.84	1.07	0.63, 1.83	0.45	0.26, 0.79	0.017
Alcohol dependency	2.35	1.52, 3.64	1.09	0.67, 1.75	0.46	0.26, 0.81	0.015

[a] VL >200 copies/mL; [b] individuals with missing values for explanatory variables were excluded; [c] Chi square test; [d] financial hardship, employment, housing status, and education; [e] employment and housing status only. PR = Prevalence Ratio; SES = socio-economic status.

8.4.5.2 *Virological rebound sensitivity analyses*

In a sensitivity analysis which additionally considered individuals who were LTFU as having experienced virological rebound, 133 (11%) MSM, 33 (19%) MSW and 60 (17%) women experienced the outcome ($p<0.0001$; log rank test). The rate of rebound was 4.6 (3.8, 5.4) per 100 person years among MSM, compared to 9.3 (6.1, 12.4), and 9.5 (7.1, 11.9) among MSW and women, respectively. This was a worst-case scenario since many of those LTFU may have simply transferred clinics; however, this data was not captured.

The results of this analysis were similar to those of the main analysis (Table 8.9). The effect sizes for women compared to MSM were larger than in the main analysis and adjustment for the other risk factors were not as able to explain the associations between gender/sexual orientation and virological rebound. However, the greater rate of rebound among women and MSW compared to MSM were still much attenuated. In particular, the model adjusted for age and all four socio-economic factors attenuated the associations to the greatest extent: the rate of rebound was attenuated by 65% and 48% for MSW and women compared to MSM, respectively.

Table 8.9: Sensitivity analysis: individuals lost to follow-up [a] considered as virological rebound [b] (N=1740)

Adjusted for [c]:	HR (95% CI)						P-value[d]
	MSW vs MSM		Women vs. MSM		Women vs. MSW		
Unadjusted	2.01	1.37, 2.94	2.06	1.52, 2.79	1.02	0.67, 1.57	<.0001
Age	2.16	1.47, 3.17	1.86	1.37, 2.53	0.86	0.56, 1.33	<.0001
SES factors							
Adjusted for age and:							
Financial hardship	1.78	1.20, 2.66	1.48	1.07, 2.04	0.83	0.53, 1.29	0.0047
Employment	1.92	1.30, 2.83	1.50	1.09, 2.07	0.78	0.50, 1.22	0.0010
Housing status	1.76	1.19, 2.61	1.53	1.12, 2.09	0.87	0.56, 1.35	0.0025
Education	2.11	1.42, 3.13	1.74	1.26, 2.39	0.82	0.53, 1.29	<.0001
Multiple SES factors							
Adjusted for age and:							
All SES factors [e]	1.51	1.00, 2.26	1.38	0.99, 1.92	0.92	0.59, 1.43	0.055
Stepwise selected subset of SES factors [f]	1.56	1.05, 2.31	1.51	1.10, 2.07	0.97	0.63, 1.49	0.011
Social circumstance factors							
Adjusted for age and:							
Country of birth	1.83	1.18, 2.85	1.52	1.02, 2.26	0.83	0.53, 1.29	0.017
English reading ability	1.96	1.29, 2.96	1.59	1.12, 2.25	0.81	0.52, 1.27	0.0016
Supportive network	2.17	1.46, 3.21	1.85	1.35, 2.52	0.85	0.55, 1.33	<.0001
Current stable partner	2.29	1.56, 3.37	1.86	1.37, 2.54	0.82	0.53, 1.26	<.0001
Mental health factors							
Adjusted for age and:							
Major depression	2.09	1.42, 3.06	1.81	1.33, 2.47	0.87	0.56, 1.34	<.0001
Major or other depression	2.10	1.43, 3.08	1.79	1.32, 2.44	0.85	0.55, 1.32	<.0001
Lifestyle factors							
Adjusted for age and:							
Recreational drug use	2.40	1.61, 3.57	2.17	1.54, 3.06	0.90	0.59, 1.40	<.0001
Alcohol dependency	2.15	1.46, 3.17	1.90	1.39, 2.59	0.88	0.57, 1.37	<.0001

[a] LTFU defined as consented longitudinal linkage and ≥1 VL measurement after questionnaire date but latest follow-up VL over eighteen months before administrative censoring date, date of rebound for these individuals is the date of but latest follow-up VL plus six months; [b] VL ≤50copies/mL at the time of the questionnaire and one subsequent VL >200copies/mL or individuals LTFU; [c] individuals with missing values for explanatory variables were excluded; [d] Chi square test; [e] financial hardship, employment, housing status, and education; [f] employment and housing status only. HR = Hazard Ratio; SES = socio-economic status.

8.5 Discussion

8.5.1 **Summary of results**

- The results presented in this chapter demonstrated that in the ASTRA study, MSW and women had poorer virological responses compared to MSM. MSW and women had 1.8 and 1.4 times greater prevalence of virological non-suppression and 2.2 and 2.0 times greater rate of virological rebound compared to MSM, respectively. In addition, women had 1.3 times greater prevalence of ART non-adherence compared to MSM. Although women tended to have a lower prevalence of virological non-suppression and lower rate of virological rebound compared to MSW, these differences were not statistically significant.
- Among the ASTRA participants, MSW and women were considerably more likely to have socio-economic disadvantage (by a range of markers) compared to MSM. This difference was most marked for current SES markers such as financial hardship and housing status compared to education.
- This is the first study to specifically assess the role of socio-economic factors in explaining gender/sexual orientation disparities in ART response. Although a few previous studies have investigated gender/sexual orientation disparities in virological outcomes, they have presented results adjusted for several covariates simultaneously, from which it was difficult to assess the specific role of SES. In the ASTRA study the differences between MSM and women were substantially 'explained' by a greater prevalence of socio-economic disadvantage among women, though there remained a relatively large PR for virological rebound. Additionally, adjustments for socio-economic factors were less able to fully attenuate virological differences between MSM and MSW. The results of this chapter give some insight into the potential reasons for gender/sexual orientation disparities in virological response to ART, suggesting that socio-economic disadvantage is an important factor, particularly for women.

8.5.2 **Interpretation of results**

The results of the present analysis showed considerable socio-economic disparities between the three gender/sexual orientation groups in the UK setting. By all markers of SES, MSM had the most favourable profile, consistent with the results of other European studies[323;324;357;364;375]. Furthermore, a greater percentage of MSW compared to women reported they were always able to afford their basic needs (28% vs. 22%), homeowners (21% vs. 15%), and university educated (36% vs. 32%). In the analyses,

disparities in socio-economic factors were more able to explain the differences in virological response to ART between women and MSM as opposed to between MSW and MSM. This could be due to the above observation that levels of socio-economic deprivation were lowest among MSM, greatest for women, and the levels for MSW were intermediate. Therefore, adjustment for socio-economic factors would tend to accentuate, rather than attenuate, poorer virological outcomes for MSW compared to women. It is also worth noting the relatively weaker role of education, compared to the other SES markers. Education tended to have less strong associations with virological outcomes (as seen in Chapter 7), show somewhat less variation between gender/sexual orientation groups, and was less effective in 'explaining' gender/sexual orientation differences in virological outcomes and non-adherence. This could provide some evidence that current financial disadvantage is a more pertinent factor than level of education.

Socio-economic factors appeared to account for much of the difference in virological response of women compared to MSM. However, socio-economic factors were less able to explain the differences between MSW and MSM it terms of virological outcomes. It implies that there may be other important differences between MSW and MSM affecting adherence not being captured by the SES variables. For example, cultural factors affecting healthcare or support seeking behaviours, stigma, or differences in comorbidities. Alternatively, factors other than non-adherence may play a larger role in poor responses for MSW than they do for women. Giving some support to this was the observation that the prevalence of self-reported ART non-adherence was similar between MSW and MSM, while it was higher for women. Possibly differences in virological outcomes between MSW and MSM may be affected by factors independent of non-adherence, such as late diagnosis (a particular issue for MSW in the UK[208]) or a higher VL at ART initiation. It was not possible to investigate this in ASTRA, as data on CD4 count at diagnosis and VL at ART initiation were not available for most participants. Equally, it was not possible to assess the extent of bias in self-reported adherence, and that this may differ between gender/sexual orientation groups.

One may expect MSW and women to have similar responses to ART because they are more comparable in terms of ethnicity, place of birth, and SES. Thus differences in observations were likely attributable to differences between genders (either biological or behavioural). In that context I found that, although self-reported ART adherence was similar among MSW and women, women had a decreased prevalence of virological non-suppression and there was some evidence of a lower rate of virological rebound among women compared to MSW. Smaller numbers of MSW and women

included in the ASTRA study mean that the comparisons of these groups were underpowered to some extent. The present chapter shows that the observed differences between these groups could not be explained by imbalances in SES, social circumstances, depression or lifestyle factors. Factors that it was not possible to measure using the ASTRA study data, such as late diagnosis or initiation of ART, may help to explain these differences.

The results suggested that socio-economic factors were less able to account for differences in the longitudinal virological rebound analysis amongst those that have achieved virological suppression at some point, than in the cross-sectional virological non-suppression analysis including all of those on ART. As the socio-economic factors were measured at the time of the questionnaire (the same time as the cross-sectional virological outcome), it is possible that they are more reflective of circumstances at that time, rather than at the time of a future virological rebound. It is also possible that different socio-economic factors will affect the ability to achieve an undetectable VL at a single point in time versus sustaining this over time to prevent subsequent rebound. There may be changes over time in socio-economic circumstance. However, while it is possible for factors such as ability to afford basic needs and employment status to change over time, this is unlikely over such a short follow-up, and particularly for socio-economic factors such as education. The differences between results for the longitudinal and cross-sectional analyses could also reflect differences in the way the analyses were conducted. For example, individuals in the cross-sectional analyses were among those who reported they were on ART at the time of the questionnaire, but these individuals could have subsequently interrupted ART over follow-up. Therefore, some of the virological rebounds may have been caused by both poorer adherence to treatment and complete treatment interruptions. In theory SES may be more able to explain poor adherence to ART than complete treatment interruptions, since there may be clinical reasons for longer treatment disruptions[657]. The cross-sectional and longitudinal analyses also differed in that individuals included in the virological rebound analysis had already achieved a VL ≤50 copies/mL, thus were likely to have been adherent to treatment at least at this time. Since socio-economic difficulties did not stop these individuals from achieving a virological suppression initially, it is possible that these factors were less important in explaining differences in subsequent virological response by gender/sexual orientation. To address this in future work, a sensitivity analysis considering only virological rebounds occurring while individuals were on ART by gender/sexual orientation could be conducted.

Besides SES, country of birth was the variable that most attenuated the differences in ART non-adherence and virological response both between MSW and MSM, and

between women and MSM. This finding, which is consistent with other European studies[364;658], indicates that poorer adherence to ART and poorer virological response to ART compared to MSM might be particularly affected by issues related to migrant status among MSW and women. This would include SES[659;660], but may also encompass factors such as language barriers[659;661], stigma[662;663], fear of deportation[659;662;664], healthcare and medication beliefs[659;665], and difficulties accessing healthcare[269].

8.5.3 **Strengths and limitations**

Although I have used the method of adjusting for socio-economic and other factors and assessing the attenuation of the gender/sexual orientation effect, other methods, such as structural equation modelling (SEMs), could have been used to address this question, and may better account for confounding and the inter-relationships between variables[666-668]. Future work could develop the use of such methods.

It is feasible that differences in ART adherence between the gender/sexual orientation groups were resultant from the likelihood of individuals to correctly self-report sub-optimal adherence[669], including reporting of adherence based on knowledge of current virological status. Self-reported adherence is a subjective measure and certain groups may perceive their adherence to be worse or better than it is in reality. Social desirability bias may affect the gender/sexual orientation groups differently: in previous studies of dietary self-report, men were likely to overestimate energy and fat intake while women were more likely to underestimate these measures[670;671]. In a study of self-reported depressive symptoms, men were less likely to report symptoms when consent forms indicated that “more involved follow-up” may occur, but that this was not true of women[670;672]. As such, men may be less likely to report ART non-adherence if they believe this is undesirable, or perhaps will lead to additional healthcare attendance or interventions. Potential bias in reporting ART adherence was suggested in the present study, as self-reported non-adherence was similar for MSW and MSM, in contrast to virological outcomes, which were poorer among MSW compared to MSM. This might suggest some sort of social desirability bias in the more subjective outcome of non-adherence. This could have implications for interpreting the results of adherence studies and adds to the existing evidence that support around adherence should not be based solely on self-reported measures, since these tend to overestimate adherence[591;673-676]. Previous studies have not studied whether this overestimation is more prevalent in certain demographic groups. Further limitations of the self-reported ART adherence measure were discussed in Section 7.5.3.

The inclusion of multiple socio-economic factors in a single model may have induced collinearity as some of the socio-economic factors were correlated with one another (see Spearman's rank correlation coefficients in Section 7.4.1). This could have reduced parameter variance estimates and affected the inferences made on whether there were differences between the gender/sexual orientation groups in this model. However, even in the models including gender/sexual orientation, age, and all four socio-economic factors, there was little evidence of multicollinearity.

As explained in previous chapters, Cox proportional hazards models could be biased by differences in frequency of monitoring of VL by gender/sexual orientation. As there were not substantial differences between the gender/sexual orientation groups in terms of median number of VL measurements per patient year of follow-up (median (IQR): 2.8 (2.2, 3.5) vs. 2.7 (2.1, 3.5) and 2.6 (2.0, 3.2) for MSM vs. MSW and women), it is unlikely that the results have been influenced by differences in the frequency of VL monitoring.

8.6 **Conclusions**

Poorer virological responses to ART were found among women and MSW compared to MSM in the ASTRA study, along with a greater prevalence of self-reported ART non-adherence among women. Gender/sexual orientation and socio-economic disparities in HIV treatment outcomes are intertwined. In particular, among people treated for HIV in the UK, socio-economic disadvantage appears to make a substantial contribution to explaining the poorer virological responses among women compared to MSM, and to explaining part of the difference for MSW compared to MSM. The results suggested that other factors might also be important for MSW: virological outcomes for this group were generally poorer than for women, even though markers of socio-economic disadvantage were somewhat less prevalent. This study is the first to focus on the ability of SES to attenuate or "explain" gender/sexual orientation disparities in virological response to ART in high-income settings. More research in this area is required to understand the mechanisms by which socio-economic factors are related to ART adherence and VL response.

Chapter 9 Prevalence of late HIV diagnosis by gender/sexual orientation and socio-economic factors

9.1 Objectives

- To present descriptive date on the trends in late and very late HIV diagnosis among individuals newly diagnosed with HIV between 2011 and 2015 attending the Royal Free Hospital, using the RFHCS.
- To assess whether demographic factors were associated with late and very late HIV diagnosis.
- To assess whether socio-economic factors were associated with late and very late HIV diagnosis.
- To evaluate HIV testing behaviours and healthcare provider missed opportunities for an earlier HIV diagnosis as potential mechanisms of any associations between demographic and socio-economic factors and late diagnosis.

9.2 Introduction

Diagnosis of HIV at a late stage continues to be a major problem even in recent years. In the UK in 2015, 39% of people newly diagnosed with HIV were diagnosed with a CD4 count <350 cells/μL[677], despite HIV testing being free and accessible to all in need. Individuals who are diagnosed with HIV at a higher CD4 count have the opportunity to initiate treatment earlier. Therefore, they are at an advantage in terms of slowing the progression of HIV[91], and improved prognosis[93;96;98]. People diagnosed late have been found to have a 10-fold increased risk of death within one year of diagnosis compared to those with a timely diagnosis[543]. Caring for individuals who have been diagnosed late tends to be complex because they are more likely to need treatment for symptomatic infections, have poorer long-term prognosis even after starting treatment (the nadir CD4 count remains a long-term predictor of clinical outcome[678;679]), and have had extended exposure to viraemia and increased immune activation[102;103]. Furthermore, it is estimated that 82% of new HIV infections among MSM in the UK are sexual transmissions from people unaware of their HIV status[213], meaning that late HIV diagnosis also contributes to ongoing transmission.

As late diagnosis is generally more common among populations who do not perceive themselves to be at a high risk of HIV infection[103;638;680-682], there are substantial variations in late diagnosis rates between demographic groups. For example in high-income settings ,individuals with demographic characteristics considered to put them

at high risk of acquiring HIV, such as MSM and people who inject drugs (PWID), are often less likely to be diagnosed late compared to those infected through heterosexual sex[111;245;543;639;683-691]. Certain groups may be less likely to test due to differing knowledge of HIV, such as migrants[692] and the elderly[693]. Additionally, migrants may be less likely to have a timely HIV diagnosis due to reduced access to healthcare services through language, stigma or cultural barriers[694], or due to diagnosis and testing patterns in their country of origin, if they were infected with HIV prior to migration[217]. Groups which are more likely to have access to routine HIV testing, such as women through routine opt out antenatal testing, may be at a reduced risk of late diagnosis[217;695].

Differences in the frequency of late diagnosis by demographic factors may also reflect disparities by SES[696]. Some European studies, including one which used data from the COHERE cohort collaboration[697], found an association between poorer SES and late diagnosis, using education level as a marker[405;639;698;699]. In contrast, the French ANRS study found that individuals on welfare benefits before HIV diagnosis had 72% lower odds of late diagnosis than those who were not, when adjusted for gender, age, year of diagnosis and other SES factors[700]. Other studies have found no evidence of an association between late diagnosis and educational attainment[406], housing[683] or employment status[699]. The association of socio-economic factors with late diagnosis may vary across geographic and healthcare settings, even within Europe, since the characteristics of the HIV-positive populations can be very different[701]. In order to better understand the relationship between SES and late diagnosis, and in turn to identify potential interventions, it may be useful to consider multiple SES markers in the same setting.

As mentioned previously, factors such as risk perception may affect HIV testing behaviours. It is important to examine the contribution both of barriers to HIV testing at the patient-level, and of missed opportunities for an earlier diagnosis at the healthcare provider-level, to the prevalence of late diagnosis of HIV[692;702]. Healthcare professionals may perceive certain groups, such as MSM, as at higher risk of acquiring HIV, and so may be more likely to offer a test as a part of routine care. Thus, some groups may have an advantage over others in accessing a timely HIV diagnosis. Of 977 individuals newly-diagnosed in January-March 2003 in the UK, 17% had sought medical care in the previous year with symptoms potentially related to HIV but remained undiagnosed[245]. Furthermore, an audit of all UK adult HIV service providers known to the British HIV Association (BHIVA) found that 25% of new diagnoses in August-September 2010 had previously had symptoms/conditions indicative of HIV but had not been tested at that time[703]. It is pertinent to consider whether missed

opportunities for earlier diagnosis are still an issue in more recent years and whether they occur more often in specific groups.

9.3 Methods

9.3.1 Study population

The study population included newly diagnosed individuals attending the Ian Charleson Day Centre (ICDC) at the Royal Free Hospital for their first visit between April 2011, when the new patient registration forms were introduced (see Appendix I.), and April 2015. Data were collected via the clinician-administered patient registration form, the details of which are described in Section 4.2.4.1 . Only individuals with completed patient registration forms were included. Data from the forms were linked to laboratory data, including CD4 counts.

9.3.2 Inclusion criteria

Individuals were required to have a recorded HIV diagnosis date that was no more than one year prior to completion of the patient registration form, to exclude those who were new to the ICDC but were transferring from other treatment centres. In addition, included individuals were required to have had at least one of the following to definitively categorise their late diagnosis status: (i) a CD4 count within three months of the date of diagnosis (either recorded on the patient registration form or by linkage to the electronic CD4 count laboratory results); (ii) an ADE before the date of diagnosis or within one month after; (iii) symptoms of seroconversion at their first visit to the ICDC; (iv) a negative HIV test within 12 months of their first positive HIV test.

9.3.3 Outcomes

9.3.3.1 *Late and very late diagnosis*

The two primary outcomes of interest were late diagnosis and very late diagnosis. The definitions were chosen to largely agree with the European Late Presenter Consensus working group definitions[704], but were modified so that individuals with missing CD4 count data who were in the primary stage of infection were not classified as diagnosed late[705]. All those who had ether a CD4<350 cells/μL within three months of the date of diagnosis or an ADE before diagnosis or within one month after diagnosis, were classified as being diagnosed late. If individuals had missing data for CD4 count at diagnosis and they had either a seroconversion illness reported at presentation to the ICDC or a previous negative HIV test within a year of the date of diagnosis, then they were categorised as not diagnosed late.

Very late diagnosis was defined similarly, but using a CD4 count cut-off of <200 cells/μL at diagnosis rather than <350 cells/μL. Therefore, the categories were not mutually exclusive (as in the European late presenter consensus definition), and 'late diagnosis' also included all individuals classified as 'very late' diagnosis.

9.3.3.2 *HIV testing behaviours and recent contact with health services*

In order to address the fourth objective of this chapter, to investigate the association between recent HIV testing behaviour and late diagnosis, three patient-level testing behaviour outcome variables were derived from responses to the following three questions on the patient registration form:

- Has the patient ever had a previous negative HIV test? (yes; no)
- Was the patient's first positive HIV test self-prompted? (yes; no)
- Was the patient's first positive HIV test in a genitourinary (GU) clinic (i.e. a sexual health clinic)? (yes; no).

The location of an individual's HIV diagnosis was included as this was thought to be indicative of perception of need for sexual health care and perception of HIV risk[706].

Additionally, four variables on recent contact with health services were derived from the following four questions:

- Has the patient been offered an HIV test in the 12 months prior to HIV diagnosis? (yes; no)
- Has the patient visited a primary care (PC) clinic in the 12 months prior to HIV diagnosis? (yes; no)
- Has the patient visited a GU clinic in the 12 months prior to HIV diagnosis? (yes; no)
- Has the patient visited an emergency department (A&E) in the 12 months prior to HIV diagnosis? (yes; no)

9.3.4 **Covariates of interest**

The following covariates of interest were considered as factors associated with late diagnosis, as defined in Section 4.4.3:

Demographic factors:

- Gender/sexual orientation (MSM; MSW; women)
- Age at diagnosis (continuous derived from date of birth and date of diagnosis)
- Ethnicity (white; black African; other)

Socio-economic factors:

- Employed (yes; no)
- Housing status (homeowner; renting; unstable/other)
- University education (yes; no)

Social circumstances:

- Children (yes; no)
- Current partner (yes; no)

HIV risk factors:

- Reported being sexually active in the last three months (yes; no)
- Reported having ever injected drugs (yes; no)
- Likely country of infection (UK; non-UK).

In absence of an individual reporting sexual activity in the last three months or injection drug use (IDU) ever, the individual was assumed to have a negative response. In contrast to Chapters 5 and 6, sexual orientation was defined using self-identified sexual orientation rather than HIV acquisition risk, as this information was available from the registration form. The group MSM includes men reporting either homosexual or bisexual orientation, and MSW includes men reporting heterosexual orientation only. The group of women includes women reporting heterosexual, homosexual or bisexual orientation. Therefore, the analyses in this chapter do not exclude individuals who had a non-sexual route of transmission.

9.3.5 **Statistical analysis**

9.3.5.1 ***Factors associated with late and very late HIV diagnosis***

The percentage with late and very late diagnosis was calculated for each of the covariates listed above. The groups were compared using Chi-squared tests or Cochran-Armitage tests for trend for ordered categorical variables.

Modified Poisson regression models[526] were used to generate prevalence ratios (PR) in order to assess the associations of each covariate with late and very late diagnosis. The association between each factor and late diagnosis was assessed in a separate model to avoid collinearity between the different markers of SES. In adjusted analyses, as in previous chapters, gender/sexual orientation and age were included in each model.

In order to reduce confounding by sexual orientation, the modified Poisson regression models were repeated in the following two subgroups: (i) MSM, and (ii) MSW and women.

9.3.5.2 *Sensitivity analysis/ missing data*

As the patient registration forms were completed during routine clinical care, time constraints meant that there were relatively high levels of missing data for some variables. It was necessary to select a method to handle the issue of missing data. The main analyses used a complete case (CC) approach. This means that individuals with complete data for a particular variable were included in analyses using that variable, therefore denominators varied between analyses. In a sensitivity analysis, the analyses described above were repeated using multiple imputation (MI). MI by chained equations[536] was performed using the "mi" package in Stata version 12[707], where the imputation-specific coefficients were combined in accordance with Rubin's rules[537]. Due to perfect prediction, it was necessary to use augmented regression. To check the variation in analysis results due to using a finite number of imputations, Monte Carlo errors (MCE) were calculated. A detailed description of this method was provided in Section 4.5.7. Data on date of HIV diagnosis, previous negative HIV tests, whether testing for HIV was self-prompted, and whether diagnosis took place in a GU clinic, were included in the imputation model as auxiliary variables. The outcome variable, late diagnosis, was also included in the imputation model although only individuals with known (non-imputed) late diagnosis status were included in the analysis. The literature suggests that the number of imputed datasets should be at least equal to the proportion of incomplete cases[536;538], thus 68 imputed datasets were created with 100 burn-in imputations before the first data set. Individuals who could not be classified as having a timely or late diagnosis (see Section 9.3.3.1) were included in the imputation model in order to provide additional information to improve the quality of the imputed values. However, under the MAR assumption, the individuals with a missing outcome variable contribute no information to the regression of the outcome variable upon the covariates[708], thus these individuals were excluded from the modified Poisson regression models.

9.3.5.3 *Prevalence of HIV testing behaviours and recent contact with health services by demographic and SES factors*

I decided to restrict analysis of these data to descriptive statistics. Thus, in order to address the secondary objective, firstly the prevalence of HIV testing behaviours and recent contact with health services were calculated and stratified by CD4 count at diagnosis (<200; 200-350; ≥350 cells/μL). Secondly, the percentage of individuals with each of the HIV testing behaviours and who had contacted health services in the year prior to diagnosis was calculated for each covariate.

9.4 **Results**

9.4.1 **Participant characteristics**

Of 888 first attendances at the ICDC between April 2011 and April 2015, 442 had been diagnosed in the previous year, were aged 18 years or older at their first visit, and were potentially eligible for inclusion in this analysis. Of these, 25 (6%) individuals were unable to be included as it was not possible to categorise their late diagnosis status definitively. Thus, 417 individuals were included.

The characteristics of the individuals included are displayed in Table 9.1. As gender/sexual orientation was defined using self-identified sexual orientation rather than HIV acquisition risk, this analysis included those infected sexually (189 (45%) sex between men and 168 (40%) heterosexual sex) as well as by other routes (12 (3%) sharing syringes/needles; 17 (4%) vertical transmission; 31 (7%) other – none by blood transfusion).

Table 9.1: Characteristics of individuals at the time of HIV diagnosis 2011-15 (N=417)

Factors		Complete case analysis		Multiple imputation analysis	
		%[a]	N	%[a]	(95% CI)
Year of diagnosis	2011	24%	104	24%	(21%, 29%)
	2012	24%	100	24%	(20%, 28%)
	2013	24%	99	24%	(20%, 28%)
	2014/2015	27%	114	27%	(23%, 32%)
	Missing	0%	0		
Demographic factors					
Gender/sexual orientation	MSM	50%	209	54%	(49%, 59%)
	MSW	18%	76	20%	(16%, 24%)
	Women	25%	105	27%	(22%, 31%)
	Missing	6%	27		
Age	Median (IQR)	40 (32, 48)		40 (32, 48)	
	Missing	0%			
Ethnicity	White	56%	234	59%	(55%, 64%)
	Black African	23%	96	24%	(20%, 28%)
	Other	15%	64	16%	(13%, 20%)
	Missing	6%	23		
Socio-economic factors					
Employed	Yes	63%	262	80%	(75%, 84%)
	No	16%	66	20%	(16%, 25%)
	Missing	21%	89		
Housing status	Homeowner	18%	76	24%	(19%, 28%)
	Renting	46%	193	60%	(54%, 65%)
	Unstable/other	12%	52	16%	(12%, 21%)
	Missing	23%	96		
University educated	Yes	34%	140	51%	(45%, 57%)
	No	29%	120	49%	(43%, 55%)
	Missing	38%	157		
Social circumstance factors					
Children	Yes	28%	117	35%	(30%, 40%)
	No	51%	214	65%	(60%, 70%)
	Missing	21%	86		
Partner	Yes	46%	190	53%	(47%, 58%)
	No	37%	155	47%	(42%, 53%)
	Missing	17%	72		
HIV risk factors					
Reported recent sexual activity	Yes	47%	197	47%	(42%, 52%)
	No	53%	220	53%	(48%, 58%)
	Missing [c]	0%	0		
Reported ever IDU	Yes	6%	26	6%	(4%, 9%)
	No	94%	391	94%	(91%, 96%)
	Missing [c]	0%	0		
Likely infected outside the UK	Yes	25%	105	37%	(32%, 43%)
	No	48%	202	63%	(57%, 68%)
	Missing	26%	110		

[a] Not all percentages add to 100% due to rounding; [c] individuals with missing values included in the "no" category; IDU= injection drug use; IQR=interquartile range.

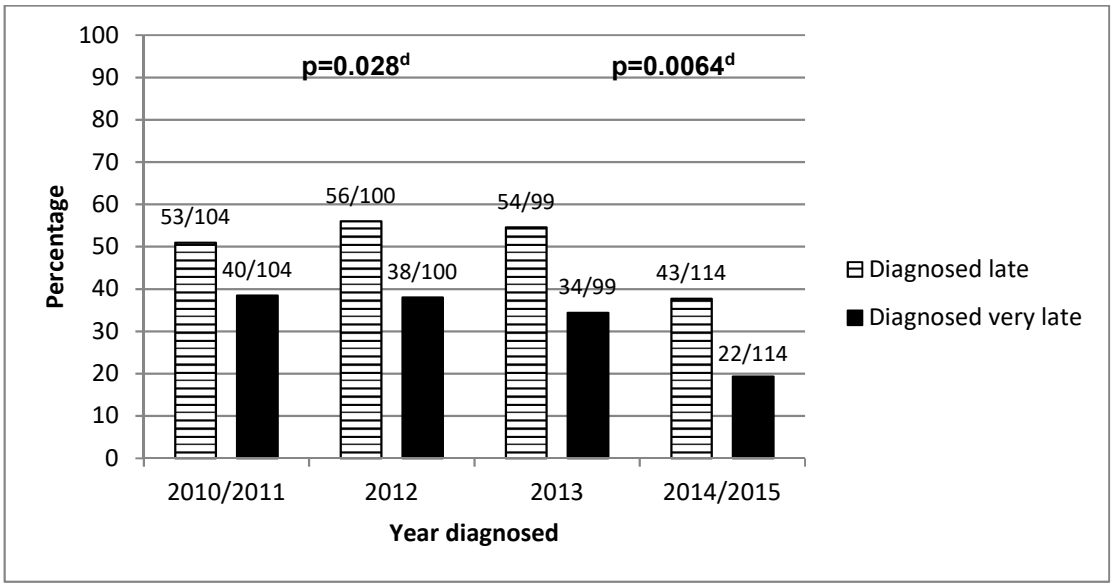
9.4.2 **Late and very late diagnosis**

9.4.2.1 ***Prevalence of late and very late diagnosis***

Approximately half of newly diagnosed individuals were diagnosed late (206/417; 49%); 187 as they had a CD4 count <350 cells/μL and 64 with a previous ADE (58 of whom had both an ADE and low CD4 count). In addition, 134/417 individuals (32%) were diagnosed very late; 121 with a CD4 count <200 cells/μL and 64 with a previous ADE. Among individuals with a recorded CD4 count within 3 months of diagnosis (N=402), the median was 353 cells/μL (interquartile range 133-574 cells/μL). Seroconversion illness was reported by 51/417 (12%) individuals and 93/417 (22%) had a negative HIV test within the last year. The percentages with late and very late diagnosis were 51% and 33%, respectively.

The prevalence of late and very late diagnosis by calendar year of diagnosis are displayed in Figure 9.1. For both outcomes, there were improvements in the most recent years. In 2014/2015, the percentage with a late diagnoses fell from 55% in 2013 to 38% in 2014/15 (p=0.014). Similarly 34% of diagnoses in 2013 were very late compared to 19% 2014/2015 (p=0.013).

Figure 9.1: Percentage of individuals diagnosed late (CD4 <350 cells/μL [a] or with AIDS defining condition [b]) and diagnosed very late (CD4 <200 cells/μL [a] or with AIDS defining condition [b]) by calendar year of diagnosis [c]



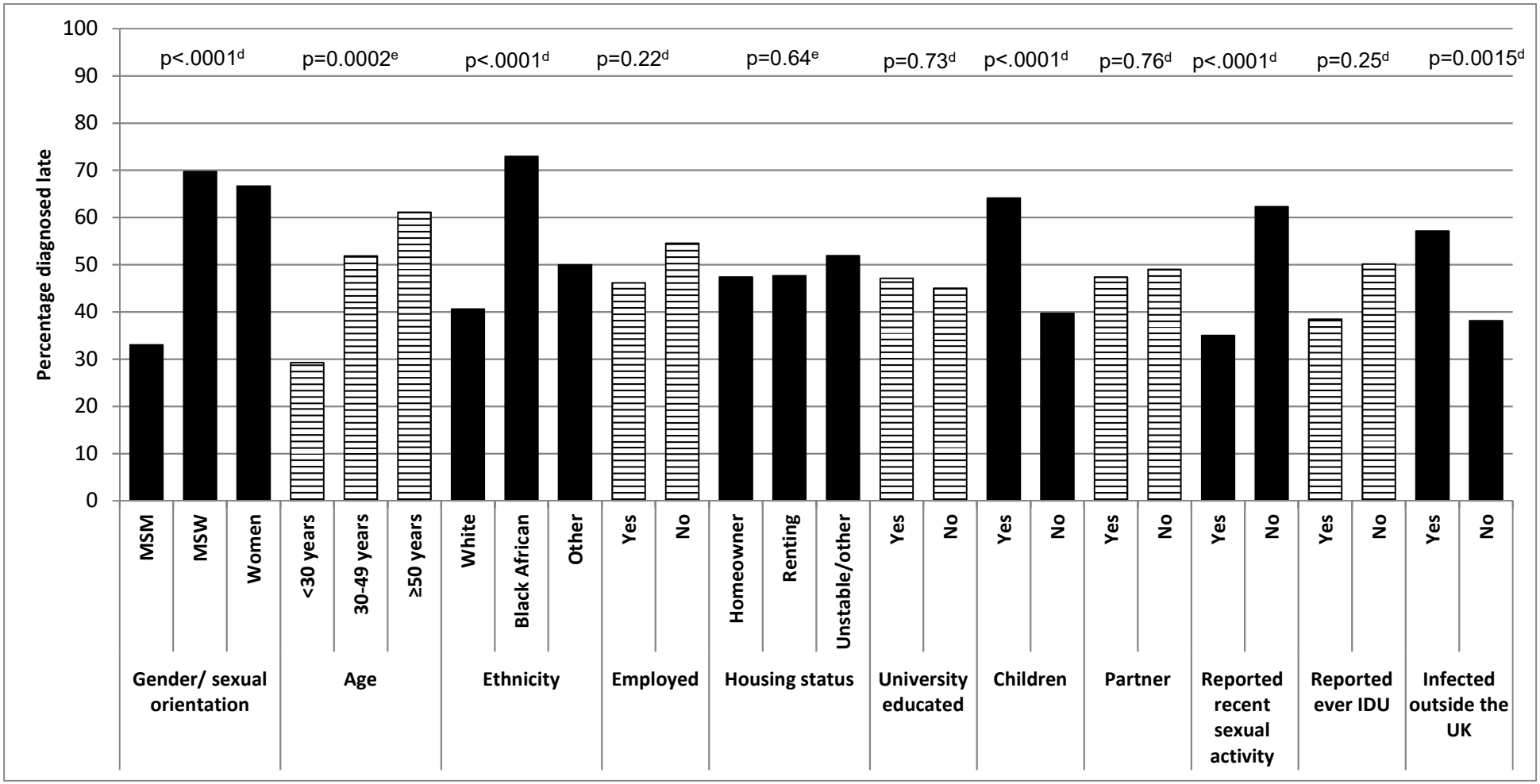
[a] Within 3 months of the date of diagnosis; [b] before diagnosis or within one month after; [c] individuals with seroconversion illness at presentation or a previous negative HIV test within a year of diagnosis were not categorised as late or very late diagnosis; [d] Chi-squared test.

9.4.2.2 ***The association of demographic, socio-economic, social circumstances, and HIV risk factors with late and very late diagnosis***

The prevalence of late diagnosis by each of the covariates is displayed in Figure 9.2. When considering demographic factors, late diagnosis was more common for MSW and women (compared to MSM), those of older age and those of black African ethnicity (compared to white/other ethnicity). I did not observe any clear differences according to markers of SES. For social circumstances, those with children were more likely to be diagnosed late, but there was no association with having a current partner. Considering HIV risk factors, individuals who did not report recent sexual activity and those with a likely source of HIV infection outside of the UK were more likely to be diagnosed late, whereas there was no statistically significant association with reporting IDU.

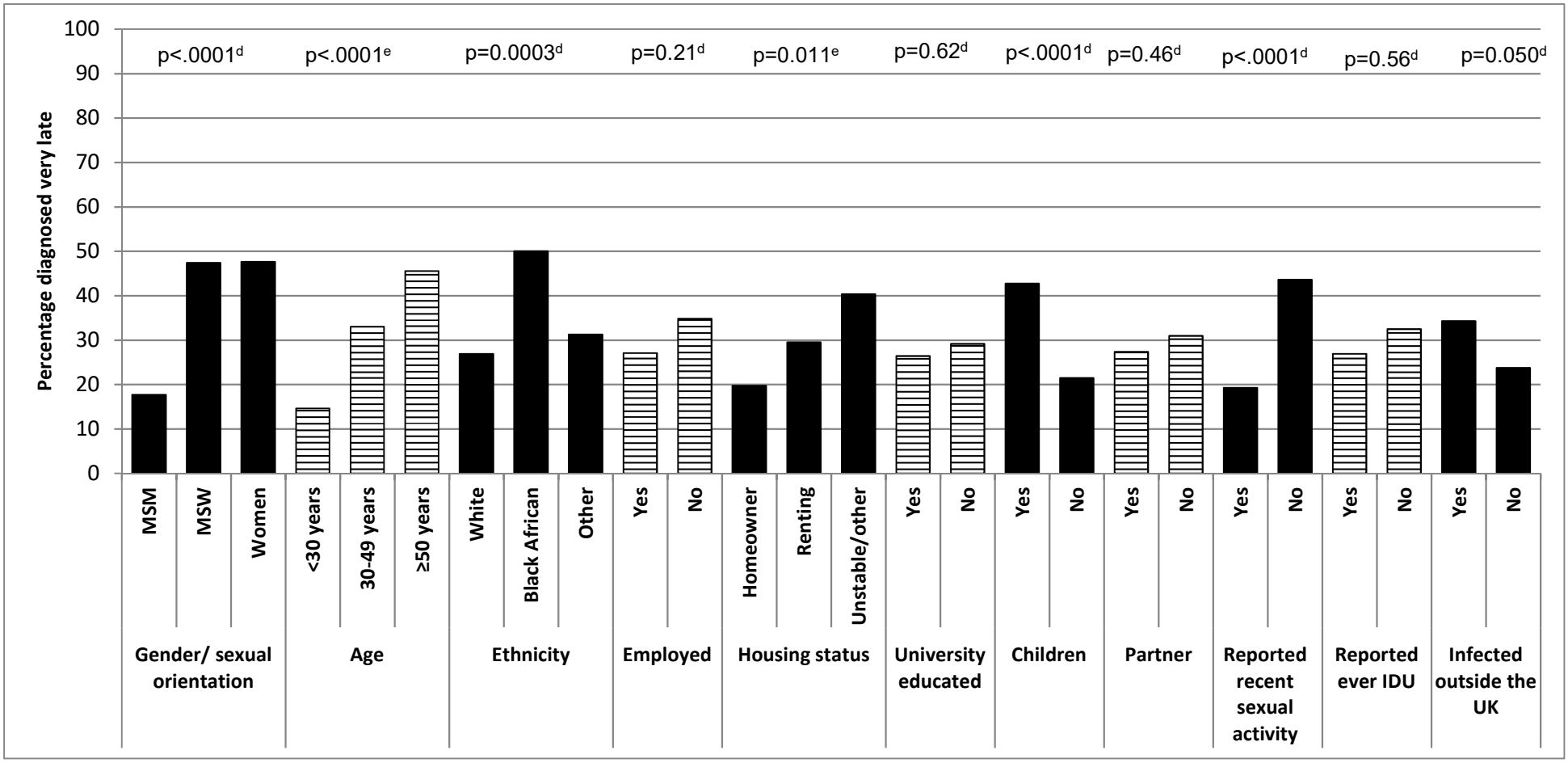
The same factors were associated with a higher prevalence of very late diagnosis, but in addition, very late diagnosis was more common among individuals with rented or an unstable housing status compared to homeowners (Figure 9.3).

Figure 9.2: Percentage with late HIV diagnosis (CD4<350 cells/μL [a] or with AIDS defining condition [b]) by potential explanatory factors (N=417) [c]



[a] Within 3 months of date of diagnosis; [b] before diagnosis or within one month after; [c] complete case analysis, for denominators refer to column one of Table 9.1; [d] Chi-squared test; [e] Cochran-Armitage tests for trend; IDU= injection drug use.

Figure 9.3: Percentage with very late HIV diagnosis (CD4<200 cells/µL [a] or with AIDS defining condition [b]) by potential explanatory factors (N=417) [c]



[a] Within 3 months of the date of diagnosis; [b] before diagnosis or within one month after; [c] complete case analysis, for denominators refer to column one of Table 9.1; [d] Chi-squared test; [e] Cochran-Armitage tests for trend; IDU= injection drug use.

The results of Figure 9.2 are also summarised in the unadjusted PRs displayed in Table 9.2. For example, MSW and women had over twice the prevalence of late diagnosis compared to MSM. After accounting for potential confounding due to gender/sexual orientation and age, most associations were attenuated. Heterosexual sexual orientation, older age, and not reporting recent sexual activity remained associated with a greater prevalence of late diagnosis in adjusted analyses and weak associations remained between late diagnosis and both likely being infected with HIV outside of the UK and being of black African ethnicity. In addition, an association with education level emerged – those who did not attend university had a 26% reduced prevalence of late diagnosis.

The unadjusted and adjusted modified Poisson regression models for very late diagnosis are displayed in Table 9.3. For most factors, these were similar to the associations with late diagnosis. Of note, both of the heterosexual groups had around 2.7 times the prevalence of very late diagnosis compared to MSM. In the analysis of very late diagnosis, there was evidence of an association with housing status, with increasing prevalence of very late diagnosis with greater housing instability: having an unstable housing situation was associated with twice the prevalence of very late diagnosis compared to homeowners. Following adjustment for gender/sexual orientation and age, similar attenuations were seen to those in the models for late diagnosis. Heterosexual orientation, older age, unstable housing situation, and not reporting recent sexual activity were associated with a greater prevalence of very late diagnosis.

Table 9.2: Factors associated with late (CD4<350 cells/μL [a] or with AIDS defining condition [b]) HIV diagnosis (N=417) [c]

Factors		N [d]	Unadjusted			Adjusted for gender/sexual orientation and age		
			PR	95% CI	P-value[e]	aPR	95% CI	P-value[e]
Gender/sexual orientation	MSW vs. MSM	-	2.10	1.65, 2.68	<.0001	1.94	1.52, 2.49	<.0001
	Women vs. MSM	-	2.01	1.59, 2.55		1.95	1.54, 2.47	
	Women vs. MSW	-	0.96	0.78, 1.17		1.00	0.82, 1.23	
Age	Per 10 years	417	1.22	1.13, 1.32	<.0001 [f]	1.16	1.07, 1.27	0.0011 [f]
Ethnicity	White	234	1		<.0001	1		0.11
	Black African	96	1.82	1.49, 2.21		1.29	1.02, 1.64	
	Other	64	1.23	0.92, 1.65		1.12	0.83, 1.52	
Employed	Yes	262	1		0.24	1		0.68
	No	66	1.18	0.91, 1.52		1.06	0.82, 1.36	
Housing status	Homeowner	76	1		0.64[f]	1		0.62 [f]
	Renting	193	1.01	0.77, 1.34		1.04	0.77, 1.40	
	Unstable/other	52	1.10	0.77, 1.56		1.09	0.79, 1.50	
University	Yes	140	1		0.69	1		0.031
	No	120	0.95	0.73, 1.23		0.76	0.59, 0.98	
Children	Yes	117	1		<.0001	1		0.35
	No	214	0.62	0.50, 0.77		1.14	0.87, 1.49	
Partner	Yes	190	1		0.72	1		0.23
	No	155	1.04	0.83, 1.30		1.14	0.92, 1.41	
Reported recent sexual activity	Yes	197	1		<.0001	1		<.0001
	No	220	1.79	1.43, 2.17		1.54	1.25, 1.92	
Reported ever IDU	Yes	26	1		0.24	1		0.40
	No	391	1.30	0.79, 2.13		1.22	0.75, 1.96	
Likely infected outside the UK	Yes	105	1		0.0019	1		0.092
	No	202	0.67	0.53, 0.85		0.81	0.63, 1.03	

[a] Within 3 months of diagnosis; [b] before diagnosis or within one month after; [c] using complete case analysis, for numbers missing for each variable refer to column one of Table 9.1; [d] number included in each model is different; [e] likelihood ratio test; [f] Cochran-Armitage test for trend; PR= prevalence ratio; aPR= adjusted prevalence ratio; IDU= injection drug use.

Table 9.3: Factors associated with very late (CD4<200 cells/µL [a] or with AIDS defining condition [b]) HIV diagnosis (N=417) [c]

Factors		N [d]	Unadjusted			Adjusted for gender/sexual orientation and age		
			PR	95% CI	P-value[e]	aPR	95% CI	P-value[e]
Gender/sexual orientation	MSW vs. MSM	-	2.67	1.83, 3.89	<.0001	2.39	1.63, 3.50	<.0001
	Women vs. MSM	-	2.68	1.88, 3.83		2.57	1.81, 3.67	
	Women vs. MSW	-	1.01	0.74, 1.37		1.08	0.79, 1.47	
Age	Per 10 years	417	1.33	1.20, 1.49	<.0001 [f]	1.24	1.10, 1.39	0.0011 [f]
Ethnicity	White	234	1		0.0007	1		0.62
	Black African	96	1.87	1.40, 2.51		1.15	0.81, 1.64	
	Other	64	1.16	0.76, 1.77		0.96	0.62, 1.51	
Employed	Yes	262	1		0.24	1		0.70
	No	66	1.18	0.91, 1.52		1.08	0.73, 1.60	
Housing status	Homeowner	76	1		0.012 [f]	1		0.021 [f]
	Renting	193	1.50	0.91, 2.48		1.69	0.99, 2.88	
	Unstable/other	52	2.05	1.17, 3.59		2.19	1.25, 3.83	
University	Yes	140	1		0.64	1		0.21
	No	120	1.10	0.74, 1.63		0.78	0.53, 1.15	
Children	Yes	117	1		0.0001	1		0.42
	No	214	0.51	0.36, 0.70		1.20	0.77, 1.85	
Partner	Yes	190	1		0.45	1		0.12
	No	155	1.14	0.82, 1.59		1.32	0.93, 1.85	
Reported recent sexual activity	Yes	197	1		<.0001	1		0.0001
	No	220	2.27	1.64, 3.13		1.82	1.32, 2.56	
Reported ever IDU	Yes	26	1		0.54	1		0.85
	No	391	1.20	0.63, 2.33		1.06	0.55, 2.04	
Likely infected outside the UK	Yes	105	1		0.060	1		0.52
	No	202	0.69	0.48, 1.00		0.88	0.61, 1.28	

[a] Within 3 months of diagnosis; [b] before diagnosis or within one month after; [c] using complete case analysis, for numbers missing for each variable refer to column one of Table 9.1; [d] number included in each model is different; [e] likelihood ratio test; [f] Cochran-Armitage test for trend; PR= prevalence ratio; aPR= adjusted prevalence ratio; IDU= injection drug use.

9.4.2.3 *Gender/sexual orientation subgroup analyses*

Table 9.4 presents the factors associated with late diagnosis in the subgroups of MSM and of MSW and women. In the subgroup of MSM, late diagnosis was more prevalent among individuals who were older, but the only other factor with evidence of an association was recent sexual activity. In the heterosexual subgroup, there was evidence of an association of late diagnosis with older age, unstable housing status, university education, having no current partner, and recent sexual activity.

Table 9.4 also presents the factors associated with very late diagnosis in the subgroups of MSM and of MSW and women. For both subgroups, the results were very similar as those seen for late diagnosis. Of note, unstable housing status was strongly associated with a higher prevalence of very late diagnosis among heterosexual individuals.

Table 9.4: Gender/sexual orientation subgroup analysis: factors associated with prevalence of late (CD4<350 cells/μL [a] or with AIDS defining condition [b]) and very late (CD4<200 cells/μL [a] or with AIDS defining condition [b]) HIV diagnosis [c]

		MSM (N=209)							MSW and women (N=181)						
		N	Late diagnosis			Very late diagnosis			N	Late diagnosis			Very late diagnosis		
			aPR[d]	95% CI	P-value[e]	aPR[d]	95% CI	P-value[e]		aPR[f]	95% CI	P-value[e]	aPR[f]	95% CI	P-value[e]
Age	Per 10 years	209	1.28	1.10, 1.49	0.0040 [g]	1.37	1.10, 1.69	0.016 [g]	181	1.09	0.99, 1.20	0.087 [g]	1.17	1.02, 1.35	0.027 [g]
Employed	Yes	145	1		0.56	1		0.64	109	1		0.90	1		0.94
	No	31	1.17	0.70, 1.95		1.23	0.55, 2.72		32	0.98	0.74, 1.30		1.02	0.65, 1.58	
Housing status	Homeowner	48	1		0.50 [g]	1		0.14 [g]	25	1		0.059 [g]	1		0.0095 [g]
	Renting	101	1.04	0.63, 1.71		2.29	0.85, 6.21		84	1.09	0.77, 1.53		1.46	0.79, 2.71	
	Unstable/ other	24	0.62	0.23, 1.71		2.15	0.52, 8.99		28	1.35	0.96, 1.89		2.15	1.15, 4.00	
University	Yes	97	1		0.22	1		0.86	41	1		0.059	1		0.074
	No	61	0.76	0.48, 1.20		1.07	0.50, 2.29		55	0.77	0.59, 1.01		0.69	0.45, 1.03	
Children	Yes	15	1		0.73	1		0.16	95	1		0.30	1		0.066
	No	158	0.88	0.45, 1.75		0.45	0.19, 1.03		52	1.15	0.88, 1.52		1.49	0.99, 2.27	
Partner	Yes	91	1		0.56	1		0.23	92	1		0.0062	1		0.0021
	No	93	0.88	0.58, 1.35		0.65	0.33, 1.32		57	1.35	1.10, 1.67		1.82	1.27, 2.63	
Reported recent sexual activity	Yes	119	1		0.030	1		0.21	75	1		0.0001	1		<.0001
	No	90	1.54	1.04, 2.27		1.45	0.81, 2.63		106	1.59	1.23, 2.00		2.13	1.43, 3.23	
Reported ever IDU	Yes	17	1		0.68	1		0.56	9	1		0.41	1		0.36
	No	192	1.15	0.56, 2.38		0.75	0.32, 1.75		172	1.27	0.69, 2.33		1.49	0.57, 3.85	
Likely infected outside the UK	Yes	43	1		0.48	1		0.48	61	1		0.11	1		0.85
	No	138	0.83	0.51, 1.35		0.76	0.37, 1.56		57	0.81	0.62, 1.05		1.04	0.69, 1.56	

[a] Within 3 months of the date of diagnosis; [b] before diagnosis or within one month after; [c] complete case analysis so number included in each model is different due to different levels of missing data; [d] adjusted for age; [e] likelihood ratio test; [f] adjusted for age and gender; [g] Cochran-Armitage test for trend; aPR= adjusted prevalence ratio; IDU= injection drug use.

9.4.2.4 ***Multiple imputation sensitivity analysis***

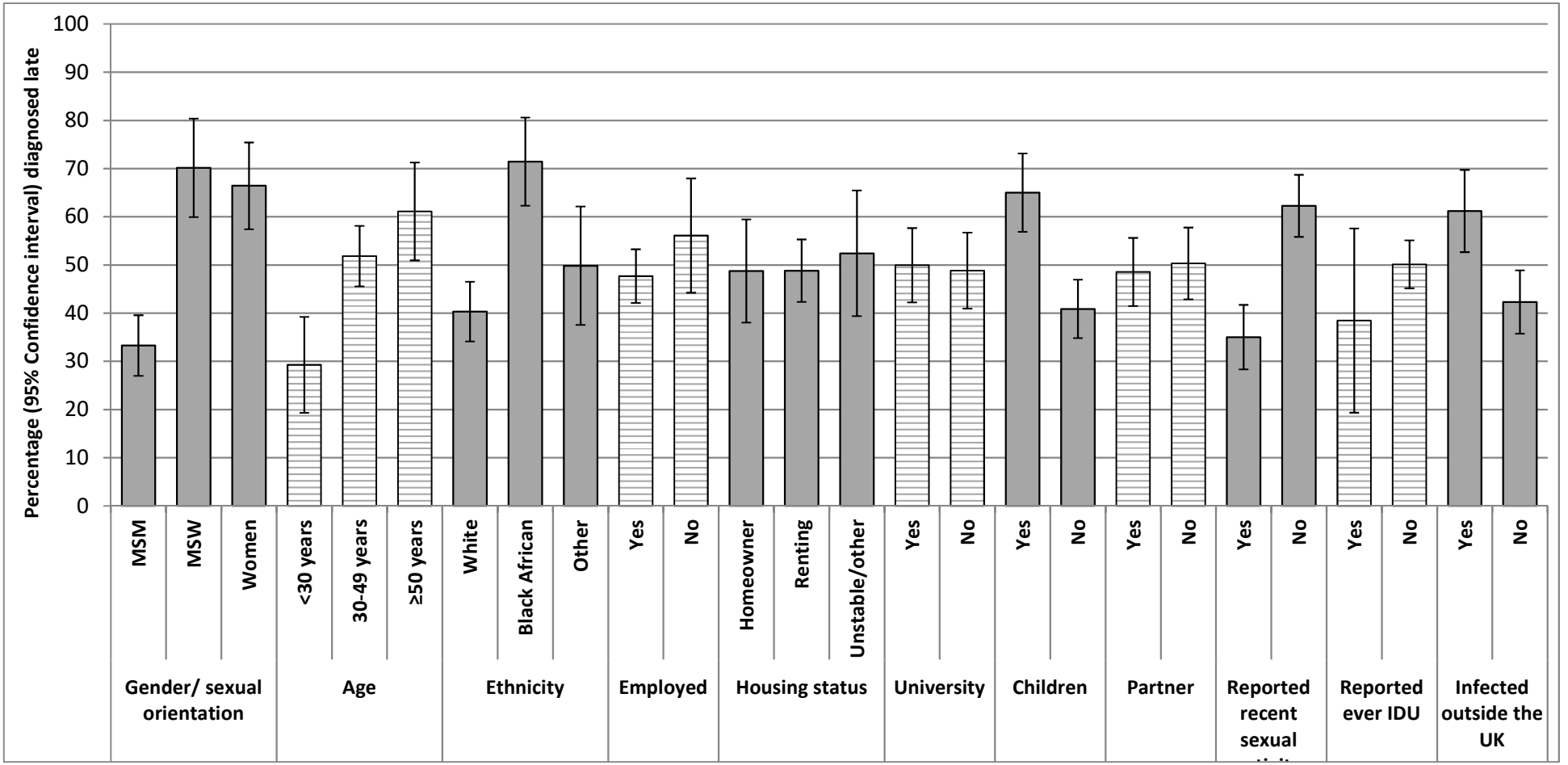
Data on gender, sexual orientation, ethnicity, employment status, housing status, education, children, current partner, and likely country of infection were missing for between 6% and 38% of individuals (Table 9.1). Of the 417 individuals included in the analysis, 220 (53%) were missing information on at least one explanatory variable and 276 (66%) were missing information on at least one variable included in the imputation model. The criteria on the MC errors specified in Section 9.3.5 were met. In addition, the MC errors of the p values were sufficiently low that additional imputations would be unlikely to change the results of the tests.

As the outcome variable was not imputed, the proportions diagnosed late, (206/417 [49%]; 95% CI: 45%, 54%), and very late (134/417 [32%]; 95% CI: 28%, 37%) were identical to the complete case analyses. The characteristics of the individuals included in the analysis following multiple imputation are shown in the last column of Table 9.1.

Figure 9.4 shows the proportion diagnosed late by each covariate. These results were comparable to those when complete case analysis was used. Similarly, the results of the analysis for very late diagnosis were consistent with complete case analysis (Figure 9.5).

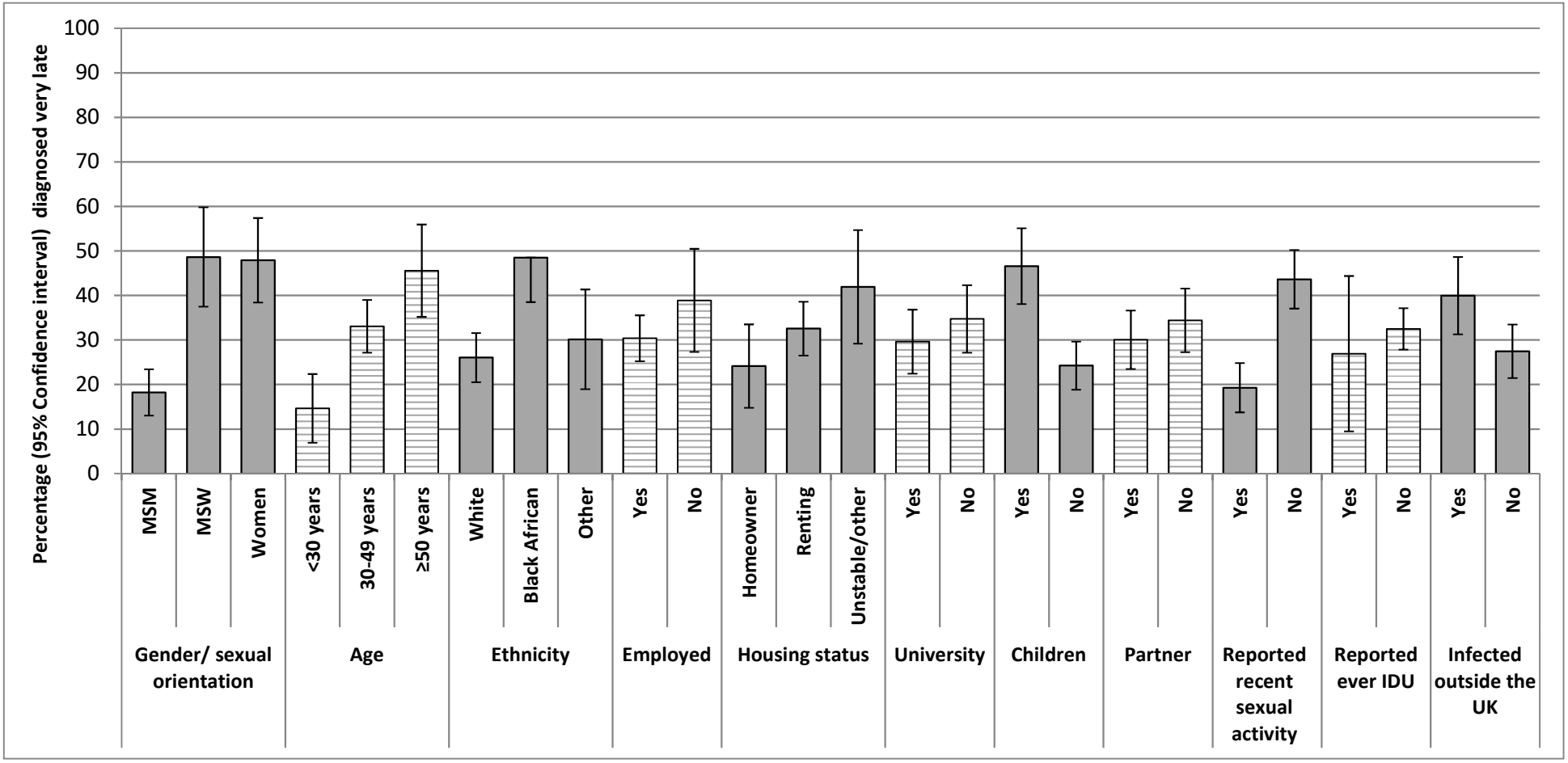
The PRs calculated from modified Poisson regression models of the multiply imputed data are consistent with those seen in the complete case analysis for both late and very late diagnosis (Table 9.5 and Table 9.6).

Figure 9.4: Multiple imputation analysis: percentage with late HIV diagnosis (CD4<350 cells/μL[a] or with AIDS defining condition[b]) by potential explanatory factors (N=417)



[a] Within 3 months of diagnosis; [b] before diagnosis or within one month after; IDU= injection drug use.

Figure 9.5: Multiple imputation analysis: percentage with very late HIV diagnosis (CD4<200 cells/μL[a] or with AIDS defining condition[b]) by potential explanatory factors (N=417)



[a] Within 3 months of diagnosis; [b] before diagnosis or within one month after; IDU= injection drug use.

Table 9.5: Multiple imputation analysis: factors associated with late (CD4<350 cells/μL [a] or with AIDS defining condition [b]) HIV diagnosis (N=417)

Factors		Unadjusted			Adjusted for gender/sexual orientation and age		
		PR	95% CI	P-value[c]	aPR	95% CI	P-value[c]
Gender/sexual orientation	MSW vs. MSM	2.11	1.66, 2.67	<0.0001	1.93	1.52, 2.45	<0.0001
	Women vs. MSM	2.00	1.58, 2.52		1.93	1.53, 2.43	
	Women vs. MSW	0.95	0.78, 1.16		1.00	0.82, 1.22	
Age	Per 10 years	1.22	1.13, 1.32	<0.0001 [d]	1.17	1.08, 1.27	<0.0001 [d]
Ethnicity	White	1		<0.0001	1		0.12
	Black African	1.77	1.45, 2.17		1.27	1.01, 1.61	
	Other	1.24	0.92, 1.65		1.09	0.81, 1.47	
Employed	Yes	1		0.21	1		0.57
	No	1.18	0.91, 1.51		1.07	0.84, 1.36	
Housing status	Homeowner	1		0.70 [d]	1		0.51 [d]
	Renting	1.00	0.77, 1.30		1.06	0.81, 1.39	
	Unstable/other	1.07	0.76, 1.51		1.12	0.80, 1.55	
University	Yes	1		0.86	1		0.062
	No	0.98	0.76, 1.25		0.79	0.62, 1.01	
Children	Yes	1		<0.0001	1		0.60
	No	0.63	0.52, 0.77		1.08	0.83, 1.37	
Partner	Yes	1		0.75	1		0.19
	No	1.04	0.83, 1.28		1.15	0.93, 1.41	
Reported recent sexual activity	Yes	1		<0.0001	1		0.0001
	No	1.79	1.43, 2.22		1.56	1.25, 1.92	
Reported ever IDU	Yes	1		0.30	1		0.43
	No	1.30	0.79, 2.13		1.22	0.75, 1.96	
Likely infected outside the UK	Yes	1		0.0013	1		0.15
	No	0.69	0.55, 0.86		0.85	0.68, 1.06	

[a] Within 3 months of diagnosis; [b] before diagnosis or within one month after; [c] Chi-squared test; [d] test for trend; PR= prevalence ratio; aPR= adjusted prevalence ratio; IDU= injection drug use.

Table 9.6: Multiple imputation analysis: factors associated with very late (CD4<200 cells/µL a or with AIDS defining condition b) HIV diagnosis (N=417)

Factors		Unadjusted			Adjusted for gender/sexual orientation and age		
		PR	95% CI	P-value[c]	aPR	95% CI	P-value[c]
Gender/sexual orientation	MSW vs. MSM	2.67	1.85, 3.86	<0.0001	2.34	1.62, 3.39	<0.0001
	Women vs. MSM	2.63	1.86, 3.73		2.50	1.76, 3.53	
	Women vs. MSW	0.99	0.73, 1.33		1.07	0.79, 1.44	
Age	Per 10 years	1.34	1.20, 1.49	<0.0001 [d]	1.27	1.14, 1.42	<0.0001 [d]
Ethnicity	White	1		0.0002	1		0.66
	Black African	1.86	1.38, 2.50		1.13	0.80, 1.58	
	Other	1.16	0.75, 1.77		0.95	0.61, 1.46	
Employed	Yes	1		0.18	1		0.49
	No	1.28	0.89, 1.83		1.13	0.80, 1.57	
Housing status	Homeowner	1		0.029 [d]	1		0.0061 [d]
	Renting	1.35	0.87, 2.10		1.54	1.00, 2.37	
	Unstable/other	1.74	1.05, 2.89		1.95	1.18, 3.21	
University	Yes	1		0.39	1		0.53
	No	1.17	0.81, 1.69		0.89	0.61, 1.29	
Children	Yes	1		<0.0001	1		0.78
	No	0.52	0.39, 0.70		1.06	0.71, 1.56	
Partner	Yes	1		0.41	1		0.10
	No	1.15	0.83, 1.59		0.77	0.95, 1.79	
Reported recent sexual activity	Yes	1		<0.0001	1		0.0002
	No	2.27	1.64, 3.13		0.54	1.35, 2.56	
Reported ever IDU	Yes	1		0.57	1		0.81
	No	1.20	0.63, 2.33		0.92	0.56, 2.08	
Likely infected outside the UK	Yes	1		0.029	1		0.59
	No	0.69	0.49, 0.96		1.09	0.66, 1.27	

[a] Within 3 months of diagnosis; [b] before diagnosis or within one month after; [c] Chi-squared test; [d] test for trend; PR= prevalence ratio; aPR= adjusted prevalence ratio; IDU= injection drug use.

9.4.3 **HIV testing behaviours and recent contact with health services**

This section focussed on the prevalence of HIV testing behaviours and recent contact with health services by demographic, socio-economic, social circumstances, and HIV risk factors with the aim of gaining understanding of why late diagnosis is more prevalent in certain groups.

9.4.3.1 ***Missing data***

Table 9.7 shows the percentage of individuals without a response recorded for the seven indicators of HIV testing behaviours and recent contact with health services. The testing factors were relatively well completed, with between 66% and 79% having a completed response. In contrast, the health services questions were not well completed – between 35% and 45% had a response recorded.

Table 9.7: Percentage missing for each HIV testing behaviour and recent contact with health services variable

		% [a]	N
HIV testing behaviour factors			
Ever negative HIV test	Yes	56%	234
	No	23%	94
	Missing	21%	89
HIV test self-prompted	Yes	45%	188
	No	34%	142
	Missing	21%	87
Diagnosed in a GU clinic	Yes	27%	114
	No	39%	162
	Missing	34%	141
Contact with health services in the last year			
Offered an HIV test	Yes	9%	36
	No	26%	109
	Missing	65%	272
Attended a PC clinic	Yes	27%	112
	No	17%	72
	Missing	56%	233
Attended a GU clinic	Yes	10%	42
	No	29%	122
	Missing	60%	253
Attended A&E	Yes	10%	43
	No	31%	129
	Missing	59%	245

[a] Not all percentages add to 100% due to rounding; PC= primary care; GU= genitourinary; A&E= accident and emergency department.

In addition, individuals with a missing response to whether they had had a previous HIV test were more likely to have been diagnosed with a CD4 count <350 cells/μL (67% vs. 45%; p=0.0001). Also, individuals with a missing response to the question on who had prompted their first positive HIV test tended to have been diagnosed with a CD4 count <350 cells/μL (59% vs. 47%; p=0.053).

9.4.3.2 *HIV testing behaviours*

Of those with a recorded response, 94/328 (29%) reported that they had not previously been tested for HIV. In addition, 142/330 (43%) reported that their HIV test was recommended by a healthcare professional or other source rather than self-prompted. Finally, 114/276 (41%) reported that they had been diagnosed in a GU clinic. Other locations of diagnoses included: 44 (16%) at PC centres; 22 (8%) in A&E; eight (3%) in antenatal care or a fertility clinic; seven (3%) in a chest or Tuberculosis clinic; two (1%) in a Hepatology clinic; nine (3%) in an infectious disease clinic; 27 (10%) in other hospital clinics; and 43 (16%) reported other locations.

A wide range of other factors were also associated with not previously testing for HIV and not self-prompting for an HIV test (Table 9.8). Those without a previous test and those who did not self-prompt were more likely to be: a heterosexual man or woman, over the age of 30 and particularly over 50 years old, of black African ethnicity compared to white ethnicity, not be employed, have an unstable housing situation compared to being a homeowner, not have a university education, have children, not report recent sexual activity, and likely infected outside the UK. Individuals of other ethnicity and individuals in rented accommodation were also less likely to self-prompt their HIV test than individuals of white ethnicity and homeowners, respectively. Being tested for HIV in a location other than a GU clinic was associated with: being a heterosexual man or woman, older age, black African ethnicity compared to white ethnicity, not being employed, having children, not reporting recent sexual activity, not reporting a history of IDU, and likely infected outside the UK.

CD4 cell count at diagnosis was strongly associated with all three markers of test seeking behaviour (Table 9.8); lower CD4 counts were associated with a much higher prevalence of not having had a previous HIV test not self-prompting an HIV test and not being diagnosed in a GU clinic.

9.4.3.3 *Recent contact with health services*

In the 12 months before their HIV diagnosis, 109/145 (75%) reported that they had not been offered an HIV test, 112/184 (61%) individuals reported that they attended a PC clinic, 42/164 (26%) individuals reported attendance to a GU clinic, and 43/172 (25%) individuals reported attendance at A&E.

A number of demographic factors were associated with having been in contact with health services in the year prior to diagnosis, with associations consistent with those for HIV testing behaviours (Table 9.9). Three of the outcome markers used (not being offered a test, attending a PC clinic and attending A&E in the previous 12 months) displayed similar associations. These were more common among: MSW and women compared to MSM, individuals over 50 years old compared to younger than 30 years, individuals renting or with an unstable housing situation compared to homeowners, non-university educated individuals, and individuals with children. In addition, individuals reporting recent sexual activity and those born in the UK were more likely to have been offered an HIV test. Attending primary care or A&E was associated with non-white ethnicity.

In contrast, the associations between potential predictive factors and being seen in a GU clinic were very different. Attendance in the previous 12 months were more common amongst: MSM, those of white or other ethnicity, individuals <30 years old, homeowners and unstably housed individuals, individuals with a university education, individuals without children, individuals without a current partner, individuals who reported recent sexual activity, individuals who reported a history of IDU, and individuals likely infected in the UK.

Ninety-four percent of those diagnosed with HIV with a CD4 count <200 cells/μL had not been offered an HIV test in the last 12 months (Table 9.9). A very high proportion of those with low CD4 counts at diagnosis had interactions with healthcare in the year prior to diagnosis; 75%, 13%, and 32% of individuals with a CD4 count <200 cells/μL had attended a PC clinic, GU clinic or A&E in the 12 months before diagnosis, respectively. For PC this percentage was significantly higher than that seen for individuals with higher CD4 counts at diagnosis.

Table 9.8: Factors associated with HIV testing behaviours [a]

Factor		No previous negative HIV test			HIV test not self-prompted			Not diagnosed in GU clinic		
		N [b]	% [c]	P-value[d]	N [b]	% [c]	P-value[d]	N [b]	% [c]	P-value[d]
Gender/sexual orientation	MSM	19/183	10%	<.0001	45/179	25%	<.0001	62/140	44%	<.0001
	MSW	32/57	56%		45/65	69%		44/57	77%	
	Women	41/77	53%		47/76	62%		51/64	80%	
Age	<30 years	10/72	14%	<.0001 [e]	16/66	24%	0.0003 [e]	25/55	45%	0.019 [e]
	30-50 years	52/194	27%		87/196	44%		94/158	59%	
	≥50 years	32/62	52%		39/68	57%		43/63	68%	
Ethnicity	White	40/192	21%	<.0001	67/192	35%	0.0004	80/153	52%	0.015
	Black African	34/68	50%		44/72	61%		47/64	73%	
	Other	15/48	31%		25/50	50%		24/43	56%	
Employed	Yes	62/238	26%	0.10	99/245	40%	0.017	114/196	58%	0.087
	No	22/60	37%		36/63	57%		39/55	71%	
Housing status	Homeowner	15/69	22%	0.019 [e]	26/72	36%	0.078 [e]	32/56	57%	0.35 [e]
	Renting	49/172	28%		79/178	44%		90/148	61%	
	Unstable/other	21/50	42%		26/50	52%		28/42	67%	
University	Yes	21/128	16%	0.0001	41/137	30%	0.0007	56/103	54%	0.32
	No	43/111	39%		58/114	51%		63/103	61%	
Children	Yes	52/93	56%	<.0001	64/103	62%	<.0001	66/91	73%	0.0041
	No	39/206	19%		69/206	34%		86/159	54%	
Partner	Yes	48/166	29%	0.96	74/173	43%	0.93	84/137	61%	0.79
	No	42/144	29%		64/148	43%		74/124	60%	
Reported recent sexual activity	Yes	43/180	24%	0.035	71/183	39%	0.083	76/144	53%	0.037
	No	51/148	34%		71/147	48%		86/132	65%	
Reported ever IDU	Yes	8/22	36%	0.41	9/23	39%	0.70	10/22	45%	0.19
	No	86/306	28%		133/307	43%		152/254	60%	
Likely infected outside the UK	Yes	35/91	38%	0.0024	52/99	53%	0.0045	58/77	75%	0.0010
	No	39/184	21%		65/185	35%		79/150	53%	
CD4 count at diagnosis	<200	42/82	51%	<.0001 [e]	66/89	74%	<.0001 [e]	65/82	79%	<.0001 [e]
	200-349	21/60	35%		25/63	40%		32/52	62%	
	≥350	30/173	17%		51/166	31%		62/135	46%	

[a] Individuals with missing values for each HIV testing behaviour factor and explanatory variable were excluded for their cross-tabulation; [b] number included in each model is different due to different levels of missing data; [c] percentages do not necessarily add to 100% due to rounding; [d] Chi-squared test; [e] Cochran-Armitage test for trend; GU= genitourinary; IDU= injection drug use.

Table 9.9: Factors associated with contact with health services in the last year [a]

Factors		Not offered an HIV test			Seen at a PC setting			Seen at a GU clinic			Seen at A&E		
		N [b]	% [c]	P-value[d]	N [b]	% [c]	P-value[d]	N [b]	% [c]	P-value[d]	N [b]	% [c]	P-value[d]
Gender/sexual orientation	MSM	43/69	62%	0.0044	50/95	53%	0.011	36/84	43%	<.0001	18/90	20%	0.26
	MSW	29/35	83%		27/41	66%		1/36	3%		13/39	33%	
	Women	33/37	89%		34/43	79%		5/39	13%		10/39	26%	
Age	<30 years	19/29	66%	0.023 [e]	22/40	55%	0.045 [e]	17/37	46%	0.0082 [e]	12/38	32%	0.41 [e]
	30-50 years	63/86	73%		64/110	58%		20/94	21%		19/101	19%	
	≥50 years	27/30	90%		26/34	76%		5/33	15%		12/33	36%	
Ethnicity	White	56/78	72%	0.79	60/105	57%	0.25	31/95	33%	0.021	21/101	21%	0.32
	Black African	28/36	78%		31/44	70%		3/35	9%		12/37	32%	
	Other	15/20	75%		17/25	68%		6/24	25%		7/24	29%	
Employed	Yes	87/117	74%	0.40	87/146	60%	0.40	34/132	26%	0.99	35/139	25%	0.63
	No	19/23	82%		21/31	68%		7/27	26%		8/27	30%	
Housing status	Homeowner	21/33	64%	0.17 [e]	23/38	61%	0.29 [e]	13/38	34%	0.71 [e]	5/37	14%	0.0078 [e]
	Renting	63/81	78%		60/105	57%		17/92	18%		24/99	24%	
	Unstable/other	18/23	78%		23/31	74%		9/27	33%		12/28	43%	
University	Yes	38/57	67%	0.099	41/74	55%	0.082	27/67	40%	0.0013	14/70	20%	0.12
	No	45/56	80%		46/66	70%		9/61	15%		20/63	32%	
Children	Yes	41/49	84%	0.070	43/59	73%	0.043	4/54	7%	0.0004	19/55	35%	0.049
	No	62/89	70%		67/117	57%		34/103	33%		22/108	20%	
Partner	Yes	62/82	76%	0.76	58/96	60%	0.87	15/89	17%	0.0063	24/93	26%	0.71
	No	44/60	73%		53/86	62%		26/73	36%		18/77	23%	
Reported recent sexual activity	Yes	55/83	66%	0.0041	64/107	60%	0.73	35/99	35%	0.0004	26/105	25%	0.93
	No	54/62	87%		48/77	62%		7/65	11%		17/67	25%	
Reported ever IDU	Yes	7/9	78%	0.85	7/11	64%	0.85	5/10	50%	0.068	2/10	20%	0.71
	No	102/136	75%		105/173	61%		37/154	24%		41/162	25%	
Likely infected outside the UK	Yes	35/40	88%	0.0082	30/49	61%	0.83	7/44	16%	0.027	12/47	26%	0.84
	No	53/82	65%		68/108	63%		33/97	34%		24/100	24%	
CD4 count at diagnosis	<200	49/52	94%	0.0001 [e]	44/59	75%	0.032 [e]	7/54	13%	0.0019 [e]	17/53	32%	0.43 [e]
	200-349	19/27	70%		17/35	49%		5/28	18%		4/32	13%	
	≥350	41/65	63%		49/88	56%		29/80	36%		21/85	25%	

[a] Individuals with missing values for each missed opportunities factor and explanatory variable were excluded for their cross-tabulation; [b] number included in each model is different due to different levels of missing data; [c] percentages do not necessarily add to 100% due to rounding; [d] Chi-squared test; [e] Cochran-Armitage test for trend; PC= primary care; GU= genitourinary; A&E= accident and emergency department; IDU= injection drug use.

9.5 Discussion

9.5.1 Summary of results

- Despite reductions in the proportion diagnosed late over time, late diagnosis of HIV continues to be a major problem in the UK[543]. In our cohort, CD4 count at diagnosis was improved in 2014-15 compared to 2011-2013; however, the prevalence of late and very late diagnosis remained high.
- There were substantial differences in the prevalence of late diagnosis between demographic groups, in particular, MSW and women had over twice the prevalence of late and very late diagnosis compared to MSM.
- As socio-economic factors are infrequently collected in a routine clinic setting, to my knowledge this is the first UK-study to look at the association of socio-economic disadvantage with late HIV diagnosis. Unlike the considerable socio-economic disparities in virological response to treatment across all markers considered in Chapter 6, late and very late diagnosis were not consistently associated with SES across all three markers. Individuals with unstable housing status had over two times the prevalence of very late diagnosis compared to homeowners and individuals without a university level education had 0.76 times the prevalence of late diagnosis compared to those with university level education. However, the inconsistency between findings from various SES markers and between the two late diagnosis definitions mean that these results should be interpreted with caution. It is possible that housing status will affect late diagnosis due to practical barriers, such as not being registered with a GP, rather than because of poorer SES.
- MSW and women were less likely to have had a previous HIV test, to self-prompt their first positive HIV test and to be diagnosed at a GU clinic than MSM. These are indications of HIV-related health-seeking behaviour and/or greater awareness of risk of HIV acquisition[699;700], and risk of STI acquisition generally[709], among MSM. Additionally, despite being more likely to have been seen in a primary care setting, MSW and women were less likely to have been offered an HIV test. This is indicative of greater missed opportunities for an earlier HIV diagnosis, among heterosexual individuals. Lower SES was associated with being less likely to have had a previous HIV test and less likely to self-prompt a HIV test.

9.5.2 Interpretation of results

The overall percentage with late diagnosis in the study population was high, which has clinical implications at the individual-level. In particular, the high percentage with CD4

count <200 cells/μL is likely to lead to significant morbidity since AIDS events are more likely once CD4 count has fallen below 200 cells/μL[710-712]. Furthermore, it is now recommended that ART be initiated as soon as possible rather than waiting for CD4 counts to fall below a certain threshold[136-138], so individuals diagnosed late will be at a greater disadvantage in terms of starting ART as their infection is at a more advanced stage.

The similar prevalence of late diagnosis among MSW and women could suggest the observed gender/sexual orientation disparities in late diagnosis were more of a cultural or demographic issue rather than a gender effect. In the UK there is a much lower overall prevalence of HIV in heterosexual population (even among black African heterosexuals) than in MSM population[208] (see Section 1.4.2.1 , so there may be less awareness of the risks of HIV in the heterosexual population. Other factors which may go some way to explaining some of the observed differences include increased health literacy among white MSM compared to black African heterosexuals[713], and a larger percentage of migrants in the heterosexual group, which in turn is associated with a number of barriers to HIV diagnosis[217;692;694].

The patterns of use of healthcare services in the year prior to diagnosis were different for MSM and heterosexual groups. MSM were much more likely to have engaged with GU clinics than heterosexual groups, who in turn were more likely to have engaged with primary care and accident and emergency care. This lends further support that the differences in timing of diagnoses observed are likely due to cultural differences between gender/sexual orientation groups rather than gender differences. Furthermore, these findings indicate that primary care and accident and emergency departments may be the most appropriate places to try to increase testing among heterosexual groups.

When assessing the association between late diagnosis and the three markers of SES in this study, there were mixed results in different directions between the measures. In addition, increasing housing instability was associated with very late HIV diagnosis but not late diagnosis. Thus, it is difficult to interpret the relationship between SES and timing of HIV diagnosis. It is possible that the markers are measuring different things, for example, educational level may affect late diagnosis through perceived risk whereas housing status may operate through access to healthcare[714;715]. It is possible that there is an association between housing status and late diagnosis as well as very late diagnosis, but that this was not detected due to lack of statistical power. Furthermore, there was evidence in the gender/sexual orientation subgroup analyses that housing status was an important factor among heterosexuals but not MSM. There

seemed to be some effect modification by sexual orientation for university education, with a borderline statistically significant association between having university-level education and a greater prevalence of late diagnosis among the heterosexual subgroup and not among MSM. Potentially this could be related to a greater prevalence of migrants among the heterosexual individuals, who despite university-level education may not have a "university-level" job once a migrant. This corresponds with our results in Chapter 8, where socio-economic factors were more able to explain poorer virological response to ART among women compared to MSM. An interaction between gender/sexual orientation and socio-economic factors with respect to late diagnosis may have masked the importance of SES among the heterosexual subgroup.

Lower SES (by all three markers) was associated with being less likely to have had a previous HIV test or self-prompt the first positive HIV test. Furthermore, each lower SES group had a lower percentage of individuals offered an HIV test in the year prior to diagnosis, although there was not a statistically significant association. There was no difference in usage of various healthcare settings in the year prior to diagnosis by employment status. However, unstably housed individuals were more likely to have attended accident and emergency departments, and individuals without a university level education were less likely to have attended a GU clinic and more likely to have attended a primary care setting. These observed differences in engagement with healthcare services indicate that interventions to target HIV testing among socio-economically disadvantaged individuals would be best placed at emergency departments or primary care settings.

Very high percentages of individuals who were diagnosed with a CD4 count <200 cells/μL had never previously tested for HIV (51%) and had not self-presented for their positive test result (74%), which suggests that individual-level factors are important drivers of late diagnosis. Possible reasons for lack of self-prompting an HIV test may include lack of perceived risk of HIV infection[716;717], fear of stigma or the consequences of a positive result[716-718], or lack of awareness of the need for regular HIV testing. Although 94% of individuals diagnosed with a CD4 count <200 cells/μL had not been offered an HIV test in the year prior to diagnosis, a large percentage reported having had interactions with primary care in the year prior to HIV diagnosis (75%). This could indicate that many instances of late diagnosis were due to missed opportunities in primary care settings, meaning that efforts to increase routine testing in this setting may be most effective.

Other than heterosexual sexual orientation, factors strongly associated with a greater prevalence of late or very late diagnosis were not being sexually active in the previous three months and likely acquiring HIV outside of the UK. The former suggests that lower perceived risk of HIV infection is likely a key barrier to achieving a timely diagnosis, while the latter may reflect testing in the respective country of HIV acquisition.

9.5.3 **Strengths and limitations**

In London in 2014, 33% of new diagnoses were with a CD4 count <350 cells/μL[543]. This was consistent with the present analysis, which found that 36% of people diagnosed in 2014 were diagnosed late (or 38% of individuals diagnosed in 2014/2015 as shown in Figure 9.1). Late and very late diagnoses in our cohort were reduced in the most recent years; similarly to the HIV-positive population across the UK. This was likely a result of increased testing, among MSM in particular[210]. In our cohort the proportions of individuals newly diagnosed with HIV by gender/sexual orientation, ethnicity and age were comparable to those found among the general population in the UK in 2014[210]. Thus, the data used in these analyses are, overall, a representative sample of the UK HIV positive population, so the conclusions made are likely applicable to the wider setting.

Although there was a large proportion of missing data in this chapter, there was data on each socio-economic factor available for at least 62% of individuals. Since information is not routinely available on SES, then there is still value in the results of an analysis that has any data on socio-economic factors in a routine care setting. It is particularly useful with regard to conclusions around associations with SES since, as mentioned in the previous paragraph, the study population is generally a representative sample of the UK HIV positive population.

Date of infection was not recorded, so CD4 count may be considered a proxy for time since infection for defining late diagnosis in this chapter. This is generally standard practice and it is defined in this way by the Consensus Working Group definition[704]. Furthermore, there was not a better marker available in this study. However, due to the variable nature of the decline in CD4 count in the absence of treatment, individuals in the “not late” group may actually have been infected a considerable time ago. Thus, they may have been exposed to viraemia and increased immune activation for long periods of time, which could have adverse clinical implications. This may also have issues from a public health point of view with respect to onwards transmission.

Since the recommendation is now to start ART as soon as the individual is ready, rather than when CD4 count has fallen to <350 cells/μL[138;139], considering anyone with a CD4 count above this level without an ADE as not diagnosed late may no longer be intuitive. The Consensus Working Group definition was defined before these new treatment recommendations, but it is possible that it is no longer relevant. However, one would need to collect data on seroconversion in order to define late diagnosis without using CD4 count as a marker, and such data was not available in the present study.

Prior to 2010, late diagnosis had been defined inconsistently in terms of different CD4 count cut-offs and clinical criteria. Since the European Late Presenter Consensus working group proposed in 2010 that "late diagnosis" be defined as a CD4 count <350 cells/μL at diagnosis, and "diagnosis at an advanced stage" to be a diagnosis with a CD4 count <200 cells/μL or with an AIDS defining event (ADE)[704], many studies have used these definitions[111;688-690;719;720]. Late diagnosis was defined in this way as it was based upon the CD4 count at which guidelines at the time stated that cART should be initiated. However, since 2015, guidelines recommend that cART be started as soon after diagnosis that an individual is ready to start[136-138], thus the current definition is now perhaps more arbitrary. In addition, an important limitation of the above definitions is that as the very early stages of HIV infection are often associated with sizable temporary declines in CD4 count[6], so individuals diagnosed during primary HIV infection may be subject to misclassification when using CD4 count alone to define late diagnosis[705]. In future studies it may be pertinent to consider individuals in primary infection (as defined by seroconversion symptoms or a recent negative HIV test) as not diagnosed late regardless of CD4 count.

It is possible that some individuals attending the Royal Free Hospital for HIV care between April 2011 and April 2015 will not have been included in the study population. If an individual did not have a completed Patient Registration Form, or it was not entered into the electronic system, then I did not have any data on them to include them in the study. However, I believe that this is unlikely to be an issue because it is a requirement for this form to be completed for national surveillance purposes. Individuals attending the Royal Free Hospital as an outpatient who either died shortly after HIV diagnosis or who died before attaining a diagnosis could have been missed from this analysis. It is not possible to estimate the extent to which this may affect my results.

Another limitation of this analysis was the proportion of missing data, although complete case (CC) analysis and multiple imputation (MI) analyses both provided

consistent results. The covariates were assumed missing at random (MAR) as it is not possible to rule out that they were in fact missing not at random (MNAR). Since the forms were clinician-completed, it is unlikely that an individual's characteristics and testing behaviours themselves were related to why they were not completed. Thus, although it was not possible to rule out that the missing data mechanism was MNAR, this was unlikely to be the case. Being diagnosed with a CD4 count <200 cells/μL was associated with having missing values for the explanatory variables. Thus, it is likely that one reason the patient registration forms were not fully completed was that the individual was ill or in need of treatment, so clinician's had other clinical priorities.

There was missing data for 54-65% of the four recent contact with health services variables therefore any imputed values for these variables would have been subject to greater uncertainty. The larger the proportion of missing data, the less likely it becomes that the data are MAR, and more likely that they are MNAR. In order to analyse MNAR data it would have been necessary to have knowledge of the reasons that the data were missing. Without this information, it was not possible to conduct CC or MI analyses for these variables, and instead only raw percentages of the individuals with recorded information could be considered.

The power to detect associations was limited in this chapter by the relatively few events in the data (206 late diagnoses and 134 very late diagnoses), particularly when considering the relatively low proportion of MSW in the study. This was demonstrated by some reasonably wide confidence intervals. Completing forms with detailed questions on SES and other factors is time consuming which could lead to a loss of data, however, gaining this detailed information is vital to understanding the reasons for delays in, and missed opportunities for, HIV diagnosis.

The gender/sexual orientation category of MSM included men who self-identified as homosexual and bisexual, and the category of women included women of any sexual orientation, which may have led to bias. Some studies have indicated that individuals who identify as bisexual may be at increased risk of late diagnosis compared to MSM[721;722]. In our study, 23 (11%) of MSM reported bisexual sexual orientation and five (5%) of women reported homosexual or bisexual sexual orientation. However, there was no evidence of a difference in the proportions diagnosed late. For other variables, there may have been misclassification of individuals. In some cases, it may be difficult to differentiate between first diagnosis and first diagnosis in the UK if the individual does not want to report previous knowledge of the condition. This could have led to over-estimation of late diagnosis due to HIV progression between these tests. Social desirability bias may also affect the accuracy of the HIV testing behaviour

variables, for example, individuals may report having previously tested for HIV because they believe that this is the answer expected of them. Some of those defined as diagnosed late might not have been HIV infected at the time of the previous healthcare encounters, and therefore factors considered, for example visit to A&E in the last 12 months, may not represent missed opportunities for diagnosis. However, the natural history of the CD4 count trajectory suggests this is unlikely to be the case for most individuals.

9.6 **Conclusions**

The results of this chapter add to the findings of the previous results chapters in this thesis to show that gender/sexual orientation, and perhaps socio-economic, disparities in HIV operate at the stage of diagnosis as well as treatment adherence and virological response. Moreover, a considerably higher prevalence of late and very late HIV diagnosis was found for both MSW and women in comparison to MSM. Both a lower probability of HIV test seeking (self-prompting an HIV test and having had a previous HIV-test) and a lower probability of having an HIV test offered by healthcare providers were apparent among heterosexual individuals compared to MSM. There was also some evidence of socio-economic inequalities in late diagnosis, but the inconsistency between measures means further work is needed to understand how different aspects of SES affect the timing of HIV diagnosis. Implementation of routine HIV testing would likely reduce the rates of late diagnoses in all groups, but is likely to have the biggest impact in groups that do not present themselves for testing or who are less frequently offered HIV tests.

Chapter 10 Summary and conclusions

10.1 Summary of main findings

The four aims of this thesis were:

1. To build an understanding of the existence of inequalities in virological response to ART by gender/sexual orientation and SES in the UK;
2. To evaluate whether these gender/sexual orientation differences have narrowed in more recent years;
3. To observe whether SES disparities contribute to any gender/sexual orientation differences in virological response;
4. To identify the relationship of gender/sexual orientation and SES with late HIV diagnosis in the UK.

The findings of my thesis against these aims were as follows:

1. Chapters 5 and 6 used data from the Royal Free HIV Cohort Study (RFHCS) and found that there was a greater prevalence of virological non-suppression among MSW and women compared to MSM. This finding was consistent in the two analysis approaches: assessing the association between gender/sexual orientation and virological non-suppression in the entire clinic population who had ever received ART, from 2000 to 2014 and assessing the association among the subset of individuals starting cART since 2000. In concordance with these results, in Chapter 8, which used data from the Antiretrovirals Sexual Transmission Risk (ASTRA) questionnaire study (2011-12), MSW and women on ART had a greater prevalence of virological non-suppression and a higher rate of virological rebound compared to MSM. In Chapter 7, I found that, in the ASTRA study, poorer SES by any of four markers considered – financial hardship, non-employment, renting or unstable housing status, or non-university education – was strongly associated with a higher prevalence of virological non-suppression, independently of demographic factors. Additionally, I found that socio-economic factors were strongly predictive of a higher rate of virological rebound among those who were virologically suppressed at the time of the questionnaire. Hence substantial inequalities in VL response by both gender/sexual orientation and SES was found in this thesis.

2. In the analyses of Chapter 5, substantial declines in the prevalence of virological non-suppression occurred from 2000 to 2006 among HIV-positive individuals on cART attending the Royal Free Hospital. There was no evidence of further reductions in the prevalence of virological non-suppression over time from 2006 onwards among individuals currently receiving cART. However, when inclusion criteria were extended to all those who ever started cART (i.e. also including those on treatment interruptions), virological response was found to be improving among MSM and women but not MSW. Although the absolute levels of non-suppression were low in recent years, there was evidence that differences between the gender/sexual orientation groups were widening over time, in relative terms. Similarly in Chapter 6, the risk of initial virological non-suppression in the first two years of ART declined over calendar year of cART initiation for all gender/sexual orientation groups. There was no evidence that the differences between MSM, MSW and women in the risk of virological non-suppression narrowed or widened with increasing calendar year of cART initiation. Therefore neither analysis provided evidence that disparities in virological response were narrowing between women, MSW and MSM and inequalities in achieving or sustaining virological suppression by gender/sexual orientation are likely to remain an important issue.

3. The analyses in Chapter 8 showed that a higher percentage of women and MSW reported being unable to afford their basic needs, being unemployed, being in temporary housing or homeless, and having no education compared to MSM. Socio-economic factors and country of birth largely explained differences between women and MSM in terms of virological response to ART, but attenuated the differences between MSW and MSM to a lesser extent. Therefore socio-economic disadvantage appeared to play an important role in explaining observed differences in virological response across gender/sexual orientation groups.

4. In Chapter 9 I considered whether gender/sexual orientation and SES disparities were also apparent for the outcome of late diagnosis, using patient registration data from the RFHCS. Among individuals newly diagnosed with HIV between 2011 and 2015, I found that MSW and women had a substantially higher prevalence of diagnosis with a CD4 count of <350 cells/μL or <200 cells/μL compared to MSM, but there was a similar prevalence of late diagnosis among MSW and women. Poorer SES using the markers of non-university education and unstable housing was associated with late diagnosis and very

late diagnosis respectively; however the associations were not consistent across the three markers of SES or two definitions of late diagnosis considered. Therefore, at the first stage in the care continuum, HIV diagnosis, MSW and women compared to MSM, and to some extent individuals with lower SES, were at a disadvantage, which could impact on the achievement of the subsequent stages of the care continuum.

10.2 **Results in context of other studies**

As I identified in Chapter 2, previous cohort studies of ART-treated individuals in France and the UK[359;364;365], and two large US-based studies of the National HIV Surveillance System[355;356], reported a greater prevalence of virological non-suppression among MSW and women compared to MSM. This is in accordance with my findings in Chapters 5, and 8. Also, a number of studies have found improved short-term virological response to ART among MSM starting ART for the first time compared to MSW and women[357-362;364], which is consistent with my findings in Chapter 6. Several previous studies comparing virological response to ART between MSW and women have found no statistically significant difference between these groups, or at least no differences after accounting for differences in characteristics at baseline [126;355;361;367;368]. This is broadly consistent with my analyses, as small and mainly non-significant differences between MSW and women were apparent in analyses of virological response in RHCS and ASTRA; in some analyses outcomes were slightly better for MSW compared to women, and in other analyses the reverse was the case. Furthermore, the results of the existing literature were largely consistent with the results of Chapters 5 and 6 in the RFHCS and of Chapter 8 using data from the ASTRA study.

Several studies using data from earlier calendar periods have found improved virological response to ART over calendar time in the HIV-positive population as a whole in high-income settings[548-550]. In a study conducted between 1999 and 2004 over the whole HIV clinic population at the Royal Free Hospital looked at the prevalence of raised VL was lowest in MSM compared to MSW and women[365]. A test for interaction in this study found no evidence of differences between black African MSW, other ethnicity MSW and MSM in trends over calendar time in raised VL[365]. In a previous study of individuals initiating ART, a test for interaction between gender/sexual orientation and calendar year of treatment initiation was considered. This study conducted on four observational databases, including the Royal Free HIV Cohort, but which took place several years ago, and therefore included only individuals

who initiated ART between 1996 and 2002[457]. In this study, the downward trend in virological non-suppression at six months among people starting ART was more rapid among MSM than heterosexuals, therefore there was evidence of widening disparities over time. The analyses in Chapters 5 and 6 were the first to consider trends in virological response to cART within gender/sexual orientation groups in recent years, when it might be expected that experience with and success of treatment had closed the gap. However, the results of these chapters showed that it is still the case that disparities between these groups are not narrowing over time. In fact, in Chapter 5 there was evidence of the differences in initial virological suppression between MSM and MSW were widening slightly over time among those who ever started cART. The analysis in this thesis extends upon previous studies in that it includes data from the last 14 years, showing that virological non-suppression continues to be a greater risk for MSW and women compared to MSM. Furthermore, in my thesis it was possible to look additionally at the moderating effect of adherence and treatment disruptions on virological response to treatment.

In concordance with the results of Chapter 6 of this thesis, women have been found to be more likely to discontinue treatment in other large European, Canadian and US-based cohort studies[126;367;571;588;609;723]. Studies which only assessed individuals initiating ART until 2002 or 2005 found either modest[457] or no evidence of[584] reductions in ART discontinuations over calendar time. In contrast, a study of 7901 individuals in Canada, found those starting ART in 2006-10 had around half the rate of treatment discontinuation or switches within three years of ART initiation compared to those starting in 1996-2000[571]. Similarly, the present analysis, which considered individuals initiating ART between 2000 and 2014, also found reductions in treatment interruptions over calendar year of ART initiation.

Chapter 2 showed that previous research focusing on the association of SES with virological response among people on ART has mainly been carried out in the US, a setting with a different system of health care to that in the UK. These studies provided considerable evidence for the importance of socio-economic disadvantage as a factor having a negative impact of ART success. In these previous studies based in the US, lower education level has been found to be strongly associated with greater odds of virological non-suppression (aOR=2.23-5.00[402;403] and aOR=1.12 for every year less education[401]). Some of these studies also found that unemployment and/or homelessness were associated with greater odds of virological non-suppression[401], at least in unadjusted analyses[400;402]. Most prior European studies of SES and virological response to ART have exclusively considered education level[126;405;406] or employment

status[342]. In these, lower education was associated with a 44% lower aOR of initial virological suppression in the Spanish CoRIS study[405], 20% lower OR in the Swiss HIV Cohort[126], and no association in the Danish HIV cohort study[406]. In the Italian ICoNA cohort, unemployment was associated with over two fold the adjusted risk of virological failure[342]. Unemployment was also found to be associated with 40% lower aOR of sustained virological suppression in the French VESPA study[359], when adjusted for factors including demographics, other socio-economic factors and ART adherence. The other markers of lower SES considered by the VESPA study, lower education and material deprivation, were associated with 40% lower OR of sustained virological suppression, however, the association with deprivation was attenuated to one in multivariable analyses[359]. Therefore most of these results from European studies, also suggest an important role of SES in virological response to ART. The results of the analyses in Chapter 7 extend upon existing literature showing strong associations of current markers of poverty and hardship, as well as lower education level, with both virological non-suppression and risk of subsequent virological rebound among people with HIV in the UK. It is interesting that, in terms of European studies, the results from the Danish HIV cohort study (based on 1178 participants) are an exception to the others, giving little evidence of an association of education with treatment outcomes in that setting[406]. There is some evidence from both Chapters 7 and 8, that education may have weaker associations with virological outcomes than markers of current poverty, and this in part may explain a lack of association in the Danish study, although the Swiss study which did find an association also only considered education. However, it is also possible that the effect of SES on ART outcomes differ across settings, even among settings of free health care. Factors such as absolute levels of poverty, the extent of social inequalities, and specifics of the health and social care systems may influence the effect of socio-economic hardship on health outcomes. Importantly, this thesis provides evidence of socio-economic disparities in adherence and virological response to ART in a UK setting, which was previously unstudied.

There is little in the existing literature about whether SES may explain gender/sexual orientation differences in virological response to ART. Thus, my results in Chapter 8 are among the first on this issue. Two European studies considered gender/sexual orientation differences in virological suppression adjusted for socio-economic factors. In a recent study of the French VESPA cohort, MSW and women on ART from sub-Saharan Africa had lower unadjusted odds of sustained virological suppression compared to MSM[359]. However, these were attenuated following adjustment for socio-economic factors, social circumstances, ART adherence and other factors. As no

results were presented unadjusted for adherence, it is not possible to isolate the effect of socio-economic factors in this study. In Chapter 8 of this thesis, adjustment for age, and four socio-economic factors attenuated the higher PR for virological non-suppression among MSW and women compared to MSM by a greater magnitude to the previous study. In a recent analysis of the Swiss HIV cohort, women had higher odds of virological suppression compared to MSW[126]. However, adjustment for education, along with a number of demographic and other factors, only led to a 5% relative attenuation in the OR of virological suppression. In contrast, women in the ASTRA study had a lower prevalence of non-suppression compared to MSW, and adjustment for education and age alone led to a relative increase in this difference by 22%. Switzerland and the UK are both settings with universal free healthcare, so one may expect similar results concerning how SES affects treatment outcomes. However, the Swiss cohort study did not include markers of current poverty additional to education. Neither of these studies, had the extent of confounding due to SES as their focus, as such they adjusted for SES and other factors simultaneously. Thus it was not possible in those studies to distinguish the effect of adjusting for education. Therefore the analysis in this thesis provides important additional insight into the underlying reasons for gender/sexual orientation differences in VL response, suggesting the critical importance of SES, particularly for women.

The analyses in Chapter 9 suggested strong disparities in the prevalence of late diagnosis by gender/sexual orientation, with considerably higher prevalence of late and very late HIV diagnosis among MSW and women compared to MSM. This was consistent with the findings from previous studies in the UK and Europe[245;683-685;689-691]. In four studies in Spain, a setting which also has a national health service, heterosexual individuals had approximately twice the odds of late diagnosis compared to MSM[111;639;686;687]. Additionally, a German study of national surveillance data among 22925 newly diagnosed individuals, found HIV acquisition through heterosexual sex was associated with 51% increased adjusted odds of late diagnosis compared to MSM[688]. With regards to the socio-economic factors, other European studies have found little evidence of an association between housing or employment status and late diagnosis[683;699]. In contrast to the findings of my thesis, several studies found that lower education was associated with a greater probability of late diagnosis[405;639;697;698]. However, in one study, welfare benefits were associated with a lower prevalence of late diagnosis[700]. Similarly, in Chapter 9, lower levels of education as a marker of poorer SES was associated with a lower prevalence of late diagnosis. The majority of previous studies looking at late diagnosis and SES only considered one marker of SES, whereas in this thesis I was able to consider three. Overall, the results of

previous studies and those in my thesis suggested a more mixed picture with regard to the association between SES and late diagnosis than is the case for the association between SES and virological response.

10.3 Strengths and limitations

10.3.1 Generalisability

All data were either from the ASTRA study or the RFHCS. Both are studies of HIV-diagnosed individuals accessing care and therefore they do not represent individuals who do not access care, however, in the UK this proportion is very low[677]. ASTRA is the largest multi-centre questionnaire based study on HIV-diagnosed individuals in the UK to date and the RFHCS is based on data from the first, and currently one of the largest, open-access HIV clinics in the UK. In terms of generalisability, the groups most affected by HIV, MSM and black African men and women, were well represented in the ASTRA study and the RFHCS[543]. However, 74% of ASTRA participants were from London clinics, and the RFHCS is based on a single centre in London. This compares to 40% of PLWH in the UK and living in London[208]. Therefore, the data may not necessarily be representative of the UK HIV-diagnosed population outside of London. Possibly, disparities in VL response across demographic and socio-economic factors may differ in less urban settings or smaller clinics. Inclusion in ASTRA was dependent on people agreeing to participate in a research study, so the ASTRA sample is necessarily a select sample. It is conceivable that socio-economic variation and differences in VL response across SES groups may be underestimated in ASTRA analysis, if socio-economic disadvantage was a barrier to participation. On the other hand, a major strength of the RFHCS is that it includes routine data from a complete clinic population making it more likely to be representative of all individuals accessing care, including those with less frequent clinic attendance, lower engagement in care, and severe socio-economic hardship. Repeating analyses of the gender/sexual orientation differences in response among two different cohorts and finding similar results suggests that the results may be generalisable.

For analysis of VL outcomes, I largely chose to use analysis techniques that are less affected by frequency of monitoring, meaning that those with good attendance were not preferentially included. I also assessed the potential impact of loss to follow-up. In Chapter 5 I found that there were similar proportions of loss to follow-up in the RFHCS among all three gender/sexual orientation groups so this was unlikely to have affected my results. Similarly, in Chapters 7 and 8 the results were consistent after considering individuals who were lost to follow-up as having had virological rebound.

Since the findings of demographic and SES variation in VL response presented in this thesis were likely to have been driven by differences in non-adherence (i.e. behavioural factors) rather than by biological differences, the results may not necessarily be generalisable across countries. The demographics of the HIV-diagnosed population varies even across other European settings. For example, in Southern Europe a significant proportion of PLWH are people who inject drugs (PWID), whereas this proportion is very low in the UK, and therefore my finings cannot necessarily be applied to this group. Systems of health care and social support may determine the extent to which demographic and SES factors impact on health outcomes. In addition, the extent of economic inequalities may vary across settings. My literature review identified studies in the US, Canada, France, Switzerland, Italy and Spain where there was evidence of consistent associations of gender/sexual orientation[126;355-357;359-361;363;364] and SES[126;342;359;363;400-405;408;415] with virological response to ART. However, such differences in virological response by SES were not apparent in the Danish HIV cohort study[406], though this study only considered education as a marker for SES, which was the measure with the least strong association with virological response in my thesis (see Section 7.5.1).

10.3.2 **Study design**

One limitation of assessing associations within observational studies is the possibility of unmeasured confounding, which it is not possible to control for. In other words demographic and SES groups may differ with respect to factors that were not measured in the database. However, there is a wealth of data collected and included in the Royal Free HIV database, so this is unlikely to be as big an issue as it would be for smaller cohort studies or multi-centre studies. It would have been interesting to consider the association of socio-economic factors with virological response to ART in the RFHCS in addition to the ASTRA study; however, these factors were not collected in the routine clinic database, except for individuals with completed patient registration forms from 2011 onwards; such an analysis may be possible using these data in the future. Even though factors such as ART adherence were not routinely collected in the RFHCS, it was possible to derive a measure from prescription data. Cohort studies also have their advantages such as the ability to consider temporal analyses and the incidence of an outcome. As it would not be possible to conduct an RCT, the gold standard, as one cannot randomise individuals to different genders or SES, cohort studies are the strongest evidence we have to establish causality.

Both the ASTRA questionnaire study and the patient registration form was that the socio-economic factors were self-reported thus they may be subject to several biases,

including social desirability bias[724], recall bias, and subjectivity[570]. However, the use of self-reported responses enables the collection of a range of individual-level socio-economic factors, which it may otherwise not be possible to obtain, for example financial hardship and housing status. Furthermore, use of alternative measures, such as the neighbourhood-based index of multiple deprivation (IMD), also have their disadvantages, such as making assumptions about individual-level SES based on group-level data[285;414]. Self-report is also one of the easiest and cheapest ways to collect adherence data[570].

10.3.3 **Missing data**

The RFHCS patient registration form hosted a wealth of questions which covered presentation details, risk behaviours, a detailed medical history, demographic factors, social circumstance factors, socio-economic factors, lifestyle factors, and encounters with UK healthcare professionals in the year before diagnosis. As such, responses recorded on this form should give a great insight into the patient at the time of registration to the Royal Free. However, this large number of questions made the form quite lengthy, at 12 pages long. Therefore analysis of this data was limited by the amount of incomplete forms, particularly with regard to the section on opportunities for an earlier diagnosis. Thus in Chapter 9 there was limited power to assess associations of demographic and socio-economic factors with the prevalence of late diagnosis. I used both complete case analyses and multiple imputation as methods to handle the missing data and the results were consistent with each method, thus were unlikely to have been biased by missing data. I could only reasonably perform descriptive analyses of individual-level and healthcare provider-level barriers to an earlier HIV diagnosis because there was a larger proportion of missing data for these variables.

There were also issues with missing data in Chapter 6, where a relatively large proportion of individuals had missing VLs and CD4 counts at ART initiation and were thus excluded (12%). I would anticipate that a large number of these individuals had transferred clinic since there are a large number of HIV clinics in London between which transfer of care is common. Nevertheless, I additionally conducted a complete case sensitivity analysis, for which the results were consistent with the main analyses. Therefore, the missing data was unlikely to have affected the results of my thesis to any large degree.

10.3.4 **Outcome measures considered**

10.3.4.1 ***Virological response measures***

In this thesis, I considered VL-based outcome measures in four of the five results chapters. I also considered the crude incidence rates for AIDS events and mortality by

gender/sexual orientation in Chapter 5. With a cure for HIV unavailable at present, preventing HIV from progressing to AIDS and then on to death are the main aims of HIV treatment. Virological response is a surrogate endpoint for these clinical outcomes. While evidence of considerable differences in VL outcomes by gender/sexual orientation or SES may not necessarily indicate large differences in clinical outcomes[725;726], identifying VL increases acts as an early indicator before drug resistance and clinical disease can develop. For instance, although, minor virological rebounds, such as a single VL >50 copies/mL or >200 copies/mL, may not necessarily be of clinical importance[564], low level viraemia is a very strong predictor of subsequent virological failure[334]. With the decreases in frequency of monitoring[603], some high VLs may be missed and therefore not be as accurate a measure of treatment response. However, sustained virological suppression has been found to be strongly associated with a lower risk of progression to AIDS or mortality[727-731]. In addition, identifying even small increases in VL may be enough to motivate another VL test may enable support to be provided to prevent the problem becoming of clinical importance. Virological response is one of the primary markers used in the clinical setting in order to evaluate success of ART. CD4 count is another primary marker of the success of treatment, however, this was only considered in the first analysis chapter of this thesis. As CD4 count may lag behind changes in VL among individuals on treatment, VL is preferred for detecting treatment failure in a timely manner in the clinic. Furthermore, virological outcomes are important not only in the context of individual-level health, but also potentially for risk of onward HIV transmission, which, in the absence of condom use, is highly dependent on VL level[13;732]. Thus, VL is used in this thesis as the most appropriate measure of current response to treatment.

10.3.4.2 ***ART adherence measures***

The ART adherence measure considered in Chapter 6 was a prescription coverage measure based on prescription refill data. Chapters 7 and 8 used self-reported responses to two questions in the ASTRA questionnaire. Both of these methods have their strengths and weaknesses. In particular, self-report can suffer from social desirability bias and the prescription based measure only evaluated the prescriptions dispensed and not that they were collected or taken. Additionally, it is possible that prescriptions could have been collected elsewhere, and therefore non-adherence may have been overestimated. However, this is unlikely as the pharmacy is within the ICDC itself and there are few specialist HIV pharmacies in London. It was only possible to assess dose adherence in this thesis; however, the results of previous UK-based studies suggest that the associations of gender/sexual orientation and SES with adherence may differ when instruction and schedule adherence is also

considered[164;374]. Despite the limitations of the adherence measures considered, poorer adherence was strongly associated with a higher risk/prevalence of virological non-suppression, which suggests that they had reasonable predictive ability of difficulties with taking ART, even if not precise measures of compliance.

10.3.5 **Covariates**

10.3.5.1 ***Gender/sexual orientation measures***

Gender/sexual orientation was defined in two ways throughout this thesis: using gender and mode of acquisition of HIV, and using gender and sexual orientation. In the former, I used reported likely sexual acquisition as a marker for sexual orientation, however, this could have led to misclassification of individuals, e.g. men who acquired HIV through sex with other men would not necessarily self-identify as gay. Furthermore, when I used self-reported sexual orientation I included bisexual men in the MSM group and women of any sexual orientation in a single group rather than separate groups. This could have led to bias of the results, however, there were very few individuals who self-reported bisexual sexual orientation.

10.3.5.2 ***SES measures***

The interpretation of the socio-economic factors is an important consideration. The analyses in this thesis do not evaluate whether an individual's education or employment status, for example, are directly causally associated with virological outcomes, and they do not elucidate the precise mechanism of the association. Thus they do not suggest that providing an individual with additional education or if an not employed individual became employed that this would affect their virological response to ART. Instead the socio-economic factors are used as markers of an individual's circumstances, i.e. lower levels of education and unemployment are indicators that an individual may currently have less access to resources and/or be exposed to greater social or economic difficulties. As this thesis considers relative SES and not absolute, the results need to be interpreted in this context. For example, the results suggest that individuals with unstable housing are at a *greater* risk of poorer virological response to ART than homeowners.

Though several socio-economic factors were considered in this thesis, income or neighbourhood-level SES factors were not collected. Collecting income data by self-report may be considered a sensitive issue, so self-reported financial hardship was collected in ASTRA instead. Gathering neighbourhood-level SES data would require postcodes to be collected which is identifiable data. Furthermore, there is mixed evidence on the use of these factors as a proxy for individual SES [285;414].

The ASTRA study only collected data on SES at a single time point. This means that an individual's socio-economic circumstances may have changed over the study period, and in particular, may not necessarily be the same at the time of the VL used to define virological rebound subsequent to the questionnaire. However, the time span was relatively short and so one may expect the markers to have remained quite constant over this time span for most participants. Therefore, the association between virological rebound and SES may have been under-estimated, as prior studies suggest that living with HIV can be associated with a decline in socio-economic resources[324;733-735].

10.4 Implications of findings

10.4.1 Implications for HIV clinical care

Gender/sexual orientation differences in initial response to first-line cART were apparent in Chapter 6 despite the UK being a setting with universal free access to care. It is important to appreciate that, although significant differences in risk of virological non-suppression across gender/sexual orientation groups remained for people starting cART in recent calendar years, the absolute differences were relatively small, with all gender/sexual orientation groups having good initial outcomes. However, as there was no evidence that the relative gender/sexual orientation disparities in treatment outcomes were lessening over time, then I would suggest that further intervention is required to minimise these differences in future. In particular, the Royal Free Hospital HIV Services have a dedicated women's clinic, which has been established for over 20 years, in which counselling and adherence support is available[508]. However, women still had poorer responses to treatment compared to MSM and had a greater prevalence of treatment disruptions and MSM and MSW. This indicates that even more needs to be done to improve HIV outcomes for women. As the women's HIV clinic already exists, one potential intervention would be to ensure women are regularly encouraged or invited to attend this clinic. Furthermore, questionnaires to ask women what could improve the service for them may be beneficial to understand what more can be done. Since peer support is currently available on the day after the women's clinic, it would be worth investigating whether having it available on the day of the women's clinic itself could positively affect the adherence of women attending the Royal Free hospital. Further study is required into the reasons for gender/sexual orientation disparities in virological response, but the results presented in this thesis suggest that such interventions should include a focus on ameliorating the impact of socio-economic disadvantage.

Interventions to reduce inequalities across socio-economic groups in treatment response and HIV diagnoses are needed. Interventions operating at a healthcare level are likely to have a limited impact on an individual's SES, as potential for impact lies predominantly with political and economic policy. However, it may be possible to mitigate the impact of socio-economic disadvantage on HIV-related outcomes. When designing clinical management strategies, the individual's personal and social circumstances should be taken into account. The results advocate a holistic approach to HIV care with linkage between clinical services and relevant social agencies to address issues related to employment, finance and benefits, immigration and housing[736]. Socio-economic interventions are particularly important since the results of Chapter 8 suggest that socio-economic disparities may go a long way to explaining differences in treatment response by gender/sexual orientation. Making HIV services more equitable may therefore help to reduce both SES and gender/sexual orientation disparities in virological outcomes. One intervention could be to provide subsidies for travel to and from HIV clinics for individuals on lower incomes[737].

Emphasis should be placed on supporting adherence of women and MSW and socio-economically disadvantaged individuals, who were identified as groups at risk of poorer adherence. At least some of the associations of gender/sexual orientation and SES with virological outcomes acted through adherence or treatment interruptions. Increasing the time before an individual switches or stops their initial treatment regimen is likely to play an important role in improving treatment adherence, lessening treatment disruptions, and in turn improving virological response to cART among individuals with poorer adherence across all gender/sexual orientation and SES groups. Although further work is still required in order to understand the drivers of poorer adherence in these groups (see Section 10.5), possible interventions to improve adherence among groups most at risk could include: prescription of less complex regimens[604] (in particular choosing antiretroviral drugs (ARVs) without food requirements/dietary restrictions[644;738-740], such as kivexa, triumeq and raltegravir- or dolutegravir-based regimens); choosing ART regimens with fewer toxicities[605]; provision of adherence support services[741], including peer support[742]; and providing additional education on the importance of adherence and consequences of non-adherence[741]. Remembering to take treatment may be another barrier to treatment adherence[743], for which pill-boxes[744;745] or text reminders[745-747] could be effective interventions. MSW, women, and socio-economically disadvantaged individuals may require closer monitoring of ART adherence, for example using MEMs caps[748;749]. Many of these are already in place, so it will be interesting to further study this issue in

the coming years to investigate its impact on response rates in the different gender/sexual orientation groups.

The results of this thesis also have implications for reducing the prevalence of late diagnosis in the UK and for reducing the gender/sexual orientation and SES inequalities in accessing a timely HIV diagnosis. Among those diagnosed with a CD4 count <200 cells/μL, 75% had visited a primary care clinic in the year prior to diagnosis and 32% had visited an emergency department, which suggests that additional allocation of resources to these settings may have an impact on reducing late diagnosis in the UK[750-752]. Opt-out HIV testing in emergency departments has been found to be acceptable and cost-effective[753]. However, in a study following the implementation of large-scale testing programs in emergency departments, lack of time and resources, as well as concerns with loss to follow-up were identified as barriers to this option[754]. Since MSW and woman compared to MSM, and individuals with poorer SES were more likely to have accessed primary care in the last year, then routine testing as a part of primary care appointments may reduce the prevalence of late diagnoses in these groups[755-759]. Prior studies have found that routine HIV testing decreased the delay from HIV infection to diagnosis[717;760-762]. Additionally, those who accessed healthcare in a setting where HIV is routinely tested for generally had a more timely diagnosis[763]. In particular, opt-out antenatal testing has led to increased diagnoses among women who may have otherwise been diagnosed at a much later stage. Routine HIV testing has been shown to be cost-effective in healthcare settings with a local HIV prevalence of >0.2%[756], and in these settings it has been recommended by BHIVA[757]. There has already been progress in this area: the Royal Free Hospital now provides opt-out HIV tests in the medical admissions unit, and the Elton John foundation has provided funding for routine HIV testing for emergency department attendees at King's College Hospital[764].

Public health campaigns to encourage regular testing are ongoing[765-767]. However, the large percentage of individuals in this study who had not had a previous HIV test (29%) suggests that further efforts to improve education and increase HIV awareness would be beneficial, particularly among those who perceive themselves at lower risk of HIV infection[762;768]. The majority of European studies have focused on barriers to HIV testing at the patient-level[717]. However, my analyses in this thesis found evidence of additional barriers to testing at the healthcare provider-level for MSW and women compared to MSM and among socio-economically disadvantaged individuals. This is likely to also be a result of cultural differences, since there is a high awareness of the importance of HIV testing among MSM. Women were much less likely to have been offered an HIV test than MSM in the year before HIV diagnosis, which indicates that

there may be missed opportunities to diagnose women at an earlier stage in their HIV infection. Previous studies have found that healthcare practitioners reported being anxious to suggest an HIV test[717;762;769]. To address this it may be beneficial to provide additional training for primary care staff, particularly in high incidence areas, in order to increase confidence in asking about sexual health. This was corroborated by the results of the Sexual Health in Practice (SHIP) study, which found substantially higher positivity rates following the educational intervention, in general practice[770].

As discussed in Section 10.3.3, the patient registration form for the ICDC collects much valuable data, however, in its current format takes time to complete. One way to improve completion rates would be to shorten the form; however, this would lead to loss of information. Alternatively, to speed up the process of completing the form, it could be re-designed to have two sections – one clinician completed and one completed by the patient. While the clinician could still complete the more clinical questions with the patient in the appointment, demographic, social circumstance, socio-economic and lifestyle questions could be self-completed in the waiting room.

10.4.2 **Implications for HIV research studies**

The results of my thesis advocate the collection of socio-economic data, both to enable future studies to examine the impact of interventions to reduce inequalities in health and as an indicator to clinicians of individuals, which may require additional support in order to achieve optimal health outcomes. This is a major implication of this thesis since previous studies in the UK have not considered the associations between SES and virological response.

While gender disparities in ART adherence and treatment response have been explored in several studies, many consider men versus women as opposed to MSM versus MSW versus women. This distinction is important since I observed substantially poorer virological response among women compared to MSM, but some evidence of improved virological response among women compared to MSW. Thus, any gender/sexual orientation differences may be masked by considering MSW and MSM as a single group. In the UK setting, evaluation of treatment responses and their predictors in these three distinct demographic groups appears a preferable strategy to use of gender and sexual orientation as two separate variables, and should facilitate the design of interventions to suit the individual needs of each group.

The issue of the correct population to consider in analyses aiming to quantify levels of virological (non-)suppression in the continuum of care is critical[771]. In different countries, the number “on ART” in the continuum of care is defined in different ways.

Within Europe, several countries consider the number who had ever started ART, (e.g. Spain; Greece; Iceland; Croatia), other countries consider those on ART when last seen (e.g. UK), and some consider individuals who had received ART at least once in a year (e.g. Italy)[771]. One of the UNAIDS "90-90-90" targets, is that by 2020 90% of individuals receiving ART should have virological suppression[221]. The results of Chapter 5 suggested that the inconsistent definition of "on ART" used by different countries for the care continuum will affect the comparability of their estimates of the prevalence of virological suppression[772]. Furthermore, these results add to the existing evidence[210] that the UK is approaching or exceeding this UNAIDS target: 89% of individuals who ever started ART and 91% of individuals on ART at the VL measurement had virological suppression in 2014. This is particularly the case since UNAIDS defines VL suppression as <1000 copies/mL rather than <50 copies/mL as used in the analyses in Chapter 5.

10.4.3 **Wider implications**

In this era of persistent economic recession, financial support for the NHS has been cut in real terms and social support services in particular have been an area specifically targeted for cost savings[773]. The results of this thesis suggest that the opposite response is needed – since socio-economic difficulties were associated with poorer adherence to treatment and poorer outcomes, greater funding for social support services could be a route to diminishing this association. This is consistent with the results of the King's Fund review, which recommended co-ordination between HIV care and social support services and that there needs to be a focus on providing access to social support services for PLWH[774].

The results of this thesis also raise the agenda of socio-economic inequalities in health in a wider context, adding to existing evidence of the adverse impact of socio-economic disadvantage on a range of health outcomes[444-446]. Socio-economic factors have not previously been incorporated in large UK clinical research studies of HIV, however, the results demonstrate that such factors may be among the most profound determinates of HIV outcomes. Reducing socio-economic inequalities in health is a priority for the National Health Service (NHS) in the UK[775], but despite this it is uncommon for socio-economic factors to be collected in routine clinical care settings[776].

In terms of routine healthcare settings in the UK, migration variables are not generally collected, thus there is a lack of information in order to understand barriers to care for migrants[777]. The associations found between country of birth and poorer health outcomes and their ability to attenuate gender/sexual orientation disparities in a HIV

setting in this thesis should raise the agenda for the collection of data on migrant status across other areas of healthcare.

Adherence to treatment is the strongest determinant of virological response to ART[199]. In contrast, for clinical outcomes such as mortality there are other factors to consider, for example the concurrent opportunistic infections[778-780], severe immunosuppression[781-783], drug-resistance[784;785], and lifestyle factors[786-793]. Thus an advantage of considering virological as opposed to clinical outcomes is that there are likely to be fewer confounders. Focussing on the narrow biomarker based-endpoint enabled me to concentrate on the behavioural differences between gender/sexual orientation and SES groups. Therefore, this thesis has implications beyond HIV, for other areas of health, which require long-term adherence to treatment to achieve improved disease prognosis.

10.5 **Further research**

The results of this thesis indicate that MSW and women (compared to MSM), and individuals with poorer SES (compared to those with higher SES) are at a disadvantage in terms of achieving specific steps of the continuum of care necessary for optimal health among PLWH: HIV diagnosis and virological suppression. However, one should not assume that these inequalities would affect each step of the care continuum in the same way. Initiation of treatment and retention in care are also extremely important stages for achieving optimal health among PLWH, but these were not the focus of this thesis. In terms of retention in care, I touched on this by performing loss to follow-up analyses and “missing=failure” analyses, however, a specific analysis focussing on this would add further insight. The recommendations of when to start ART have changed a number of times in recent years making it difficult to assess disparities in timing of ART initiation[50;133;134;136;137;142]. Furthermore, gender comparisons may be complicated by ART use during pregnancy. However, the results of the START trial[460] and subsequent change in recommendations such that all HIV diagnosed individuals should initiate ART regardless of CD4 count[138;139], mean that factors associated with the time between HIV diagnosis and ART initiation will be of increasing importance in the coming years. Future research should consider inequalities at these points of the care continuum.

Evaluating why women and individuals of poorer SES are less adherent to ART is key to understanding the barriers to virological suppression in these groups. A qualitative study may be best able to capture in depth behavioural information on the

mechanisms by which gender/sexual orientation and SES affect adherence in order to drive further quantitative work. It is possible that the reasons for inequalities in adherence to ART, a lifelong treatment, are similar to those for other long-term treatments, so such analyses could have wide implications.

In this thesis, women were more likely to have cART disruptions during the first 12 months of cART, thus understanding the drivers to this is key to ensuring virological response improves in this group. The most frequent reason recorded for cART disruption in Chapter 6 of this thesis was toxicity for all gender/sexual orientation groups. This was similarly the case in several other studies[189;362;794]. Of the reasons given by women for treatment disruptions in Chapter 6, 8.2% were pregnancy related. To gain more detailed information on the causes of disparities in adherence and treatment disruptions, qualitative studies of the reasons for these behaviours and targeted studies to assess the effectiveness of the aforementioned interventions by gender/sexual orientation group[723] would be required.

Women account for about a third of those infected in the UK[105] but they are often underrepresented in HIV research[339;795;796]. This is true in clinical trials in all areas of medicine[797-801], and in particular, black women have been shown to have even greater barriers to entering RCTs[802]. Often it is not possible to draw gender-based conclusions from clinical trials since the numbers of women included are too small. This situation does not appear to be improving in more recent years[803] and is unlikely to improve in the future, unless the reasons for non-participation in these groups are explored. I wanted to address this as a part of this thesis. I considered a qualitative, interview-based study and designed questions for this and for a survey. I discussed the potential for this analysis with physicians at the King's College Hospital and the Royal Free Hospital as they were planning to conduct a study (BESTT trial). However, the period for the trial exceeded the period for completing my thesis. An insight of why women do not participate in HIV clinical trials would likely translate into reasons that women do not participate in RCTs more generally. This could have a long-term impact of ensuring that RCTs can be more representative of the population and more able to detect gender differences in efficacy and safety of new drugs. Thus, I recommend that a study of reasons for non-participation among women be conducted.

The introduction of strategies such treatment as prevention (TasP) to prevent sexual acquisition of HIV has led to reductions in HIV transmission and fewer clinical events[149]. Since there is evidence of greater awareness of such strategies among MSM compared to heterosexuals[804], it is possible that if TasP is successful, then HIV diagnoses would fall more rapidly among MSM compared to MSW and women.

Awareness or uptake of such methods would likely increase HIV awareness generally, thus studies should consider the effect TasP might have on disparities in prevalence of HIV diagnosis and late diagnosis.

Women have lower mortality than men in the general population and one would expect to find a similar pattern in HIV studies. While some previous studies have found no difference in clinical outcomes by gender[330;335;805;806], others have found evidence of higher standardised[807;808] or unstandardised[809] mortality rates among women compared to men. In the modern cART era, life expectancy is increasing for PLWH[93;98], with individuals experiencing fewer AIDS events and more non-AIDS events[810;811]. A recent European study of the ART Cohort Collaboration (ART-CC) found that gender differences in mortality increasingly resemble those in the general population, as a result of this increasing importance of non-AIDS events for which there are greater gender differences[812]. In Chapter 5, I found that MSW had a higher rate of AIDS and mortality than MSM and women in most calendar years, however, I was unable to assess whether there were differences between the groups in trends over time due to lack of clinical events. Using a larger dataset, it would be of interest to assess whether the gender/sexual orientation inequalities I observed in virological outcomes are also apparent for clinical outcomes, with particular emphasis on assessing trends over time in AIDS and mortality by gender/sexual orientation.

The results for MSW were more uncertain than for the other groups since there were smaller numbers in this group. Given that throughout this thesis MSW have poorer outcomes than MSM, and at times poorer outcomes compared to women, further study of this currently understudied group would be warranted. There are certain barriers that may be more of an issue for MSW than in the other gender/sexual orientation groups, for example there is anecdotal evidence of greater stigma among MSW[813-815]. Since differences in ART response between MSW and the other gender/sexual orientation groups remained after adjustment for socio-economic, social circumstances, or lifestyle factors in this thesis, future research should consider the role of other factors, such as stigma, in predicting treatment response among MSW. Additionally, adherence was not found to be poorer among MSW compared to MSM in the self-reported measures from the ASTRA study, despite the consistent finding that MSW had poorer responses to treatment than MSM throughout this thesis. Therefore, it is essential to assess whether there are other important factors influencing virological response among MSW or whether the measures of adherence used are not accurately capturing adherence for this group.

There are measures of socio-economic difficulties or difficult circumstances that it may be useful to consider in future studies. In this thesis, I found that several markers of SES were strongly associated with treatment adherence and response, thus having a number of these socio-economic issues concurrently may affect treatment adherence and response over and above any of the single markers of SES. Therefore, it may be of interest for a future study to consider composing a measure which incorporates the extent of socio-economic difficulties by combining several SES markers[816;817]. One of the SES markers considered in this thesis was education, however, the results of Chapters 7 and 8 in this thesis suggested that education may not be as representative of SES as markers of current poverty, such as financial hardship and housing status and may also reflect levels of health literacy. Evaluation of the association of education with virological response to treatment over and above the more current measures would help to understand the mechanism by which SES affects treatment outcomes. Stress has been shown to be associated with poorer SES[818;819], and as such future studies may consider whether poorer responses to ART were due to greater levels of stress among socio-economically deprived individuals. US-based studies have found that the incidence of stressful life events is associated with poorer treatment adherence[820-823]. Furthermore, cumulative stressful life events were associated with increased odds of virological non-suppression[820] and increases in VL[824], though another study found no association between interventions to improve stress and VL[825]. Therefore, the effect of stressful life events should be considered in a UK setting. Another area that may warrant further attention is repeated measures of SES. SES is not fixed over time and some socio-economic factors, such as employment status, can change over a relatively short period. Multiple measurements of SES over time could not be studied as a part of my thesis since there was not a follow-up questionnaire for ASTRA and socio-economic factors are not currently collected as a part of routine care appointments. An analysis of repeated measures of socio-economic factors, ART adherence, and VL would reduce confounding and help to assess whether there is a true causal relationship between SES and adherence, and in turn with virological ART response[826].

In the HIV-positive population, it can be difficult to disentangle the effects of gender, sexual orientation, ethnicity, culture, and SES. Nonetheless, I studied this issue in Chapter 8 of this thesis, and found evidence suggesting that SES was a stronger predictor of virological response to ART compared to gender/sexual orientation. It would be of interest to conduct a case-control study, using RFHCS data, to investigate the association between specific socio-economic circumstances and virological rebound among those on ART for six months. A group of cases would be selected who

were experiencing VL rebound and compared to a similar group of controls who were virologically suppressed. In particular, such a study could assess the role of socio-economic circumstances and life events occurring around the time of virological failure. The study could also consider whether the SES factors associated with improved VL response were different for each gender/sexual orientation group.

With better understanding of the mechanisms that mediate the effect of lower SES on non-adherence and VL outcomes, interventions could be developed. Subsequently, an RCT could be designed to assess whether and which socio-economic interventions would reduce SES and gender/sexual orientation disparities in virological response to ART, or whether other interventions are needed over and above this, for example adherence-based interventions. Besides studies of the efficacy of these interventions, a cost effectiveness analysis of the allocation of resources should be conducted in order to assess which areas should be targeted to make the most impact on reducing inequalities in HIV outcomes.

With the introduction of self-testing, the rise in rapid point-of-care testing in recent years, and the interventions from the London HIV Prevention Programme, one may expect a fall in late diagnoses, as HIV tests are increasingly accessible and convenient[827]. It is possible that this will affect some gender/sexual orientation or SES groups more than others though. For example, individuals without stable housing will be unlikely to benefit as much from the availability of self-testing from home. On the other hand, those finding it difficult to test for HIV may benefit most from strategies which make HIV testing more convenient, therefore they may reduce gender/sexual orientation or SES disparities in late diagnosis. Future studies should look at changes over time in late diagnosis by gender/sexual orientation and SES. Specifically one should consider the disparities in late diagnosis in a subset of individuals who were diagnosed with HIV by self-testing or rapid point-of-care testing.

Since the number of individuals included in the analyses in Chapter 9 was quite small, additional years of accumulated data would allow a more in-depth analysis of factors associated with missed opportunities for an earlier HIV diagnosis. Moreover, due to the small absolute number of late diagnosis events in the present analysis, it would be interesting to repeat all analyses with the additional data collected in this time. At this point, it may be possible to make further inferences about the relationship between late diagnosis and socio-economic factors.

There is evidence that individuals diagnosed during community-based point of care testing are less likely to be diagnosed late than those diagnosed at a GU clinic[828].

Previous studies have indicated that there has been a shift from HIV being diagnosed in GU clinics towards community-based centres and primary care[829]. Since the results of this thesis show more women and MSW were seen in primary care in the year prior to diagnosis compared to MSM, it would be interesting in future to assess whether increased testing in this area leads to reductions in the gender/sexual orientation disparities in late diagnosis. This may also apply to socio-economic disparities, since non-university educated individuals were more likely to have attended primary care services in the year before HIV diagnosis.

10.6 **Concluding remarks**

I have shown that, in the UK, HIV treatment outcomes are generally excellent and improving over calendar time. However, in both the RFHCS and the ASTRA study there were considerable relative differences by gender/sexual orientation and SES. Demographic and socio-economic risk factors for poorer treatment adherence could be screened for at ART initiation so that clinicians can try to link these individuals with the services to address these problems[830]. SES explains at least part of gender/sexual orientation inequalities in treatment outcomes; therefore, it is all the more important to collect this information as a part of routine care and, in turn, to provide personalised HIV care plans. In terms of wider dissemination of results from my thesis, some of the results have already been included as a part of regular parliamentary briefings on the current situation of PLWH in the UK and published in peer-reviewed journals with further publications planned. I hope that the results from this thesis may have some influence on government policy with regards to allocation of resources/funding to integrate social and financial support services into HIV care[831], particularly in the current climate of the UK with increasing and competing demands on health and support service resources[832;833]. In addition, the evidence provided in this thesis may help to prioritise a focus on socio-economic factors in clinical research of HIV and other chronic conditions.

Appendix I. Patient registration form at the Royal Free Hospital

NEW PATIENT REGISTRATION

1. PATIENT DETAILS

1.1 Hospital No. ☐☐☐☐☐☐☐☐

1.2 Date of Visit: ___/___/___

1.3 Private Patient: ☐ Yes ☐ No

1.4 Personal details:

Surname: _____ Date of Birth: ___/___/___

First Name: _____ Country of Birth: _____

Sex: ☐ Male ☐ Female Date of arrival in the UK: ___/___/___

1.5 Ethnic group:

☐ White British	☐ Mixed other (specify)	☐ Black Caribbean
☐ White Irish	.....	☐ Black African
☐ White other	☐ Indian	☐ Black other
☐ White and Black Caribbean	☐ Pakistani	☐ Chinese
☐ White and Black African	☐ Bangladeshi	☐ Other (specify) .....
☐ White and Asian	☐ Asian other	.....

1.6 Patient's address:

Stage 1 interviewer: _____ Is a stage 2 interview required? ☐ Yes ☐ No

Full Postcode: ☐☐☐☐☐☐☐

1.7 Contact details:

Tel: _____

Mobile: _____

Work: _____

Email: _____

1.8 Next of kin details:

Name: _____

Address: _____

Tel: _____

Aware of diagnosis? ☐ Yes ☐ No

1.9 GP details:

Is the patient registered with a GP? ☐ Yes ☐ No

If YES:

Name: _____

Address: _____

Tel: _____

Is GP aware of diagnosis? ☐ Yes ☐ No

Can GP be contacted? ☐ Yes ☐ No

1.10 a. Height:	m/ft/in	
b. Weight:	kg	

2. PREVIOUS CENTRES OF HIV/AIDS CARE (if applicable)		
2.1 Is this patient a transfer?	☐ Yes ☐ No	
2.2 If YES, where from?	☐ Royal Free private patient ☐ UCH/ Mortimer Market ☐ St Mary's ☐ Bart's/Royal London ☐ King's ☐ North Middlesex ☐ Blood Transfusion Service	☐ Kobler/C&W ☐ St Thomas's ☐ Whittington ☐ Guy's ☐ Barnet General ☐ Other (specify) .....
2.3 Can last centre be contacted?	☐ Yes ☐ No	2.3.1 Hospital No. ☐☐☐☐☐☐☐☐

3. PRESENTATION AND RISK BEHAVIOUR		
3.1 a. Has patient ever had a NEGATIVE HIV antibody test?		☐ Yes ☐ No
b. If NO, has the patient ever declined an HIV antibody test?		☐ Yes ☐ No
c. If YES, how many NEGATIVE HIV antibody tests had patient had, before first ever POSITIVE antibody test?		☐☐ times tested HIV neg.
3.2 a. LAST NEGATIVE antibody test:	Date: ___/___/___	
Where was this test performed?	☐ General Practice ☐ Royal Free SDTC ☐ Royal Free Marlborough ☐ Royal Free Antenatal ☐ UCH/ Mortimer Market ☐ St Mary's ☐ Bart's/Royal London ☐ King's	☐ North Middlesex ☐ Kobler/C&W ☐ St Thomas's ☐ Whittington ☐ Guy's ☐ Barnet General ☐ Blood Transfusion Service ☐ Other incl. non-UK (specify) .....
b. FIRST EVER POSITIVE antibody test:	Date: ___/___/___	
Where was this test performed?	☐ General Practice ☐ Royal Free SDTC ☐ Royal Free Marlborough ☐ Royal Free Antenatal ☐ UCH/ Mortimer Market ☐ St Mary's ☐ Bart's/Royal London ☐ King's	☐ North Middlesex ☐ Kobler/C&W ☐ St Thomas's ☐ Whittington ☐ Guy's ☐ Barnet General ☐ Blood Transfusion Service ☐ Other incl. non-UK (specify) .....
3.3 a. Who prompted the FIRST POSITIVE HIV antibody test:	☐ a. Patient her/himself ☐ b. Health care provider (incl. blood donation services) ☐ c. Insurance/Visa screen ☐ d. Other (specify)	
b. If health care provider, which setting:	☐ a. General Practice ☐ b. A & E ☐ c. GU/STD clinic ☐ d. Antenatal clinic ☐ e. Chest/TB clinic	☐ f. Hepatology clinic ☐ g. Fertility clinic ☐ h. Other infectious disease clinic ☐ i. Other hospital clinic ☐ j. Other (specify).....
3.4 Is the patient presenting with a seroconversion illness?	☐ Yes ☐ No	
3.5 Evidence of recent infection from avidity assay (or similar antibody test)	☐ Yes ☐ No	

3.6 HIV RISK BEHAVIOUR		
3.6.1 Most likely reason(s) for HIV infection: (Please tick MORE THAN ONE box, if applicable)	☐ a. Had shared syringes/needles ☐ b. Sex between men without a condom ☐ c. Heterosexual sex without a condom ☐ d. Had oral sex without a condom ☐ e. Had blood transfusion ☐ f. Vertical transmission ☐ g. Needle stick injury ☐ h. Other (specify)	
3.6.2 a. Patient presumed infected in the UK?	☐ Yes ☐ No ☐ Not known	
b. If NO, in what country/region?		
3.6.3 a. Is there a likely identified source partner?	☐ Yes ☐ No	
b. If YES, what is source partner's likely country/region of infection?		
c. What is the likely route by which source partner was infected? (Please tick MORE THAN ONE box, if applicable)	☐ i. Had shared syringes/needles ☐ ii. Sex between men without a condom ☐ iii. Heterosexual sex without a condom ☐ iv. Had oral sex without a condom ☐ v. Had blood transfusion ☐ vi. Vertical transmission ☐ vii. Needle stick injury ☐ viii. Other (specify)	
3.7.4 Patient defined sexual orientation:	☐ Homosexual ☐ Heterosexual	☐ Bisexual ☐ Other: .....
3.7.5 a. Has the patient ever injected drugs (shared needles/syringes)?	☐ Yes b. If YES: ☐ No	Year first injected: Year last injected:
3.7.6 Is the patient currently sexually active?	☐ Yes ☐ No	
3.7.7 In the last 3 months has the patient: (Please tick MORE THAN ONE box, if applicable)	☐ a. Been sexually active ☐ b. Had sex without a condom with someone with unknown or negative HIV status ☐ c. Had sex without a condom with MORE THAN ONE partner ☐ d. Shared drug using equipment/needles/syringes ☐ e. Had a sexually transmitted infection diagnosed	
3.7.8 Date of most recent STI screen:	a. Date: ____/____/____	☐ b. Never had one

4. MEDICAL HISTORY

HIV-RELATED

4.1 Has the patient ever been diagnosed with AIDS?	☐ Yes ☐ No
4.2 Does the patient currently have any HIV-related symptoms (including oral candida, herpes zoster, etc)?	☐ Yes ☐ No

4.3 Complete below for any NEW or PREVIOUS AIDS Diagnosis

Please tick the AIDS indicator disease (s) and give month and year of first diagnosis

AIDS Indicator Disease	Diagnosis		Date	AIDS Indicator Disease	Diagnosis		Date
	Definitive	Presumptive	Mth/Yr		Definitive	Presumptive	Mth/Yr
a. Candidiasis: trachea, bronchi, or lungs	☐	NA	/	n. Lymphoma, Burkitt's, or equivalent term	☐	NA	/
b. Candidiasis: oesophageal	☐	☐	/	o. Lymphoma, immunoblastic or equivalent term	☐	NA	/
c. Cervical carcinoma, invasive	☐	NA	/	p. Lymphoma, primary in brain	☐	☐	/
d. Coccidioidomycosis: expulmonary	☐	NA	/	q. Mycobacterium avium: extrepulmonary	☐	☐	/
e. Cryptococcosis: expulmonary	☐	NA	/	r. M.tuberculosis: pulmonary	☐	☐	/
f. Cryptosporidiosis with diarrhoea > 1 month	☐	NA	/	s. M.tuberculosis: extrepulmonary	☐	☐	/
g. Cytomegalovirus retinitis	☐	☐	/	t. Mycobacterium of other or unidentified species disseminated	☐	☐	/
h. CMV disease not liver, spleen, or nodes	☐	NA	/	u. Pneumocystis carnii pneumonia	☐	☐	/
i. Encephalopathy (dementia) due to HIV	☐	NA	/	v. Pneumonia recurrent within 12 months	☐	☐	/
j. Herpes simplex: ulcers > 1 month or bronchitis, pneumonitis, oesphagitis	☐	NA	/	w. Progressive multifocal leukoencephalopathy	☐	NA	/
k. Histoplasmosis: disseminated/extrepulmonary	☐	NA	/	x. Salmonella septicaemia, recurrent	☐	☐	/
l. Isosporiasis with diarrhoea for > 1 month	☐	NA	/	y. Toxoplasmosis of the brain	☐	☐	/
m. Kaposi's sarcoma	☐	☐	/	z. Wasting syndrome due to HIV	☐	☐	/

4.4 CD4 COUNTS AND VIRAL LOADS

a. Patient's MOST RECENT CD4 count:	Value:	Date: ___/___/___	☐ Never had one
b. Patient's MOST RECENT viral load:	Value:	Date: ___/___/___	☐ Never had one
c. If patient transferred in, PRE-THERAPY viral load (if applicable)	Value:	Date: ___/___/___	☐ Never had one
d. LOWEST ever CD4 (if known)	Value:	Date: ___/___/___	☐ Never had one

4.5 CURRENT AND PAST ANTITRETROVIRALS

Drug	Dose	Started	Stopped	Reason
a.		Date: ___/___/___	Date: ___/___/___	
b.		Date: ___/___/___	Date: ___/___/___	
c.		Date: ___/___/___	Date: ___/___/___	
d.		Date: ___/___/___	Date: ___/___/___	
e.		Date: ___/___/___	Date: ___/___/___	
f.		Date: ___/___/___	Date: ___/___/___	
g.		Date: ___/___/___	Date: ___/___/___	
h.		Date: ___/___/___	Date: ___/___/___	

4.6 NON-HIV RELATED MEDICAL HISTORY

DIAGNOSES

	Ever diagnosed?	If YES, date of diagnosis:
a. Hepatitis B	☐ Yes ☐ No ☐ Unknown	Date: ____/____/____
b. Hepatitis C	☐ Yes ☐ No ☐ Unknown	Date: ____/____/____
c. Hypertension	☐ Yes ☐ No ☐ Unknown	Date: ____/____/____
d. Diabetes	☐ Yes ☐ No ☐ Unknown	Date: ____/____/____
e. Coronary revascularisation	☐ Yes ☐ No ☐ Unknown	Date: ____/____/____
f. MI	☐ Yes ☐ No ☐ Unknown	Date: ____/____/____
g. Stroke	☐ Yes ☐ No ☐ Unknown	Date: ____/____/____
h. Chronic renal failure	☐ Yes ☐ No ☐ Unknown	Date: ____/____/____
i. Renal dialysis	☐ Yes ☐ No ☐ Unknown	Date: ____/____/____
j. Liver cirrhosis	☐ Yes ☐ No ☐ Unknown	Date: ____/____/____
k. Osteopenia	☐ Yes ☐ No ☐ Unknown	Date: ____/____/____
l. Osteoporosis	☐ Yes ☐ No ☐ Unknown	Date: ____/____/____
m. Psychiatric illness	☐ Yes ☐ No ☐ Unknown	Date: ____/____/____
n. Non-AIDS cancer[1] Site of cancer:	☐ Yes ☐ No ☐ Unknown	Date: ____/____/____
x. Other (specify)	☐ Yes ☐ No ☐ Unknown	Date: ____/____/____

4.7 CURRENT NON-ANTIRETROVIAL MEDICATION

Drug	Dose	Purpose
a.		
b.		
c.		
d.		
e.		
f.		
g.		

CONCOMITANT TREATMENTS

4.7.1 Is the patient CURRENTLY prescribed, or taking regularly without a prescription, any of the following medication?

☐ No → SKIP to 4.8

☐ Yes

4.7.2 Please indicate which medication (MARK ALL THAT APPLY).

☐ a. Drugs that lower blood pressure * →	☐ i. Beta blockers ☐ ii. Diuretics ☐ iii. Angiotensin converting enzyme (ACE) inhibitors	☐ iv. Angiotensin receptor blockers (ARBs) ☐ v. Calcium channel antagonists ☐ vi. Other
☐ b. Lipid lowering drugs * →	☐ i. Fibric acid ☐ ii. Statins (HMG-CoA reductase inhibitors) ☐ iii. Bile acid sequestrents	☐ iv. Nicotinic acid ☐ v. Cholesterol absorption ☐ vi Fish oils ☐ vii. Other
☐ c. Drug treatment for diabetes mellitus * →	☐ i. Insulin ☐ ii. Metformin ☐ iii. Sulfonylureas	☐ iv. Thiazolidinediones ☐ v. Biguanides ☐ vi Other
☐ d. Hormonal therapy * →	☐ i. Hormonal contraceptive ☐ ii. Hormone replacement therapy ☐ iii. Thyroid replacement therapy ☐ iv. Megestrol acetate	☐ v. Growth hormone ☐ vi. Tamoxifen ☐ vii. Arimidex ☐ viii. Other ** Mark all that apply*

☐ e. Anti-coagulant drugs ☐ f. Nitrates ☐ g. Aspirin/acetylsalicylic acid (> 2 weeks) ☐ h. Other non-steroidal anti-inflammatory drugs ☐ i. Anabolic steroids (including transdermal) ☐ j. Systemic corticosteroids ☐ k. Immunomodulators ☐ l. Cancer chemotherapy	☐ m. Methadone, prescribed ☐ n. Other opiates, prescribed ☐ o. Anti-epileptic drugs ☐ p. Benzodiazepines ☐ q. Anti-depressants ☐ r. Anti-psychotic drugs (neuroleptics) ☐ s. Other drugs for bipolar mood disorder	☐ t. Drug treatment for osteoporosis ☐ u. Proton pump inhibitors ☐ v. H2 blockers ☐ w. Anti-CMV drugs ☐ x. Drug treatment for herpes simplex ☐ y. Systemic anti-fungal drugs ☐ aa. Anti-MAC drugs ☐ bb. Anti-PcP/anti-PjP drugs

[1] Excluding non-melanoma skin cancer

4.7.3 Please indicate if the patient has been taking any of the following medication?		
☐ a. Anti-tuberculosis drugs	☐ Currently ☐ In the past year	Specify drug(s):
☐ b. Drug treatment for hepatitis B	☐ Currently ☐ In the past year	Specify drug(s):
☐ c. Drug treatment for hepatitis C	☐ Currently ☐ In the past year	Specify drug(s):

4.8 Previous surgery	Date of operations	Details:
	a. Date: ___/___/___	
	b. Date: ___/___/___	
	c. Date: ___/___/___	
	d. Date: ___/___/___	
	e. Date: ___/___/___	
4.9 Gynaecological history (e.g. smear test)		
4.9.1 Date of most recent smear test:	Date: ___/___/___	
4.10 Is the patient currently covered by vaccinations against:	☐ a. Hep B	
	☐ b. HPV	
4.11 Known allergies:		
4.12 Family medical history (e.g. diabetes, heart disease, DVT, cancer)		
4.13 Family history of MI and/or stroke in a first degree relative diagnosed before age 50?	☐ Yes ☐ No	

5. BACKGROUND CHARACTERISTICS

5.1 PARTNER STATUS

a. Does patient currently have a partner?	☐ Yes ☐ No	aa. ☐ More than one current partner
b. If YES, is partner:	☐ Male ☐ Female	
c. If YES, is partner known to be HIV positive?	☐ Yes ☐ No ☐ Unknown	
e. Marital/Civil partnership status	☐ Single ☐ Married/Civil partnership ☐ Separated/Divorced ☐ Regular cohabiting Male ☐ Regular cohabiting Female ☐ Widowed/Partner died	

5.2 REPRODUCTION

a. Does patient have any children?	☐ Yes ☐ No	
b. If YES, how many?	☐ 1 ☐ 2 ☐ 3 ☐ 4 or more	
c. Are any HIV positive?	☐ Yes ☐ No ☐ Unknown ☐ None tested so far	d. If YES, where are they being treated?
e. Additional pregnancy history (e.g. mode of delivery)		

5.3 CONTRACEPTION [FOR WOMEN ONLY]

a. Has the patient ever used contraceptive methods?	☐ Yes ☐ No	
b. Is the patient currently using:	☐ i. Condom ☐ ii. Pill ☐ iii. IUD ☐ iv. Injectables ☐ v. Implants ☐ vi. Female condom ☐ vii. Diaphragm	☐ viii. Foam/Jelly ☐ ix. Lactational Amen. Method ☐ x. Rhythm Method ☐ xi. Withdrawal ☐ xii. Female sterilisation ☐ xiii. Male sterilisation ☐ xiv. Other Method (specify) .....

5.4 SOCIO-ECONOMIC CHARACTERISTICS

5.4.1 Housing

Is the patient:	☐ An owner occupier ☐ Renting from the local authority ☐ Renting privately ☐ Other (specify)	
5.4.2 Employment		
At present is the patient: (please tick more than one box, if applicable)	☐ a. In paid employment or self-employed ☐ b. Unemployed and looking for work ☐ c. Retired ☐ d. Looking after family or home	☐ e. In full-time education ☐ f. Lack of work permit ☐ g. Unable to work because of long-term sickness or disability
5.4.3 Education		
At what level did patient complete education?	☐ No qualifications ☐ 0 levels/GCSE or equivalent ☐ A levels/ or equivalent	☐ University degree or above ☐ Other qualifications (please specify) .....
5.5 LIFESTYLE		
5.5.1 a. Has patient ever smoked cigarettes regularly (at least 1 per day)?	☐ Yes ☐ No	**b. If YES:** Number of years: .....
c. Is patient currently a smoker?	☐ Yes ☐ No	**d. If YES, how many cigarettes per day:** .....
5.5.2 a. Has the patient ever been a regular heavy drinker (on average > 6 units per day) over a period of years?	☐ Yes ☐ No	**b. If YES:** Number of years: .....
c. If YES, is patient currently a regular heavy drinker?	☐ Yes ☐ No	
d. Has patient ever received treatment for an alcohol problem from a physician or treatment programme?	☐ Yes ☐ No	
5.5.3 a. In the last 3 months has the patient used recreational drugs?	☐ Yes ☐ No	**b. If YES, which?**

5.6 ANY FURTHER INFORMATION ON SOCIAL CIRCUMSTANCES

6. FOR PATIENTS NEWLY DIAGNOSED WITH HIV: ENCOUNTERS WITH UK HEALTH CARE PROVIDERS IN THE YEAR PRIOR TO HIV DIAGNOSIS*
* i.e. not including the encounter at which diagnosis was made

6. FOR PATIENTS NEWLY DIAGNOSED WITH HIV: ENCOUNTERS WITH UK HEALTH CARE PROVIDERS IN THE YEAR PRIOR TO HIV DIAGNOSIS*		
* i.e. not including the encounter at which diagnosis was made		
6.1 a. In the year prior to HIV diagnosis, how many times has the patient visited a GP?	☐ 0 ☐ 1	☐ 2-3 ☐ > 3
b. In the year prior to HIV diagnosis, how many times has the patient visited A & E?	☐ 0 ☐ 1	☐ 2-3 ☐ > 3
c. In the year prior to HIV diagnosis, how many times has the patient visited STD/GU clinic?	☐ 0 ☐ 1	☐ 2-3 ☐ > 3
d. In the year prior to HIV diagnosis, has the patient presented at any health care setting with flu-like symptoms:	☐ Yes ☐ No	
6.2 a. In the year prior to HIV diagnosis, has the patient been offered an HIV test prior to the first positive test? (if YES, respond for MOST RECENT test offered)	☐ Yes, test refused ☐ Yes, result negative	☐ Yes, result not known ☐ No
b. If YES, where was the test offered: (Please tick MORE THAN ONE box, if applicable)	☐ a. General Practice ☐ b. A & E ☐ c. GU/STD clinic ☐ d. Antenatal clinic ☐ e. Chest/TB clinic	☐ f. Hepatology clinic ☐ g. Fertility clinic ☐ h. Other infectious disease clinic ☐ i. Other hospital clinic ☐ j. Other (specify).....
6.3 a. In the year prior to HIV diagnosis, has the patient been under the care of any hospital clinic for any condition?	☐ Yes ☐ No	
b. If YES, at which clinic? (Please tick MORE THAN ONE box, if applicable)	☐ Hepatology ☐ Respiratory ☐ Oncology ☐ Renal ☐ Cardiology ☐ Psychiatry ☐ Gynaecology	☐ Obstetrics ☐ Endocrinology ☐ Orthopaedics ☐ Dermatology ☐ Ophtalmology ☐ Haematology ☐ Other (specify) ....

7. CLINICAL EXAMINATION		
7.1 Examinations	Value	Notes
a. Blood pressure	___ / ___	
	Normal	Abnormal findings
b. General	☐	
c. Cardiovascular	☐	
d. Skin	☐	
e. Chest	☐	
f. Mouth	☐	
g. Abdomen	☐	

h. Lymph nodes	☐	
i. Neurological/Fundi	☐	

7.2 INVESTIGATIONS (BLOOD TESTS) ARRANGED (Please tick)	
a. First visit blood tests sent:	☐ Yes ☐ No
b. First visit STI screen:	☐ Yes ☐ No
c. Additional investigations arranged:	

7.3 REFERRALS		
Referrals:	☐ Lymphoma	☐ Lipid Clinic
	☐ Opthalmology	☐ Hepatitis Clinic
	☐ Renal	☐ Women's Clinic
	☐ Psychology	☐ Other .....
	☐ Psychiatry	.....

8. SUMMARY OF CASE	
01.	
02.	
03.	
04.	
05.	
06.	
07.	
08.	
Letter to GP? ☐ Yes ☐ No	Next visit in: _____ weeks
Doctor's name:	

Post:	
Contact bip/ext:	

9. PATIENT CONSENT

Request for consent for use of clinical information for research and development

Patient should be provided with a copy of the following information:

The information that we obtain as part of the care we give you is held on a computerised database. Occasionally this information, without your name attached, is combined with data from patients in other hospitals. Analysis of these databases can help to answer questions about how best to care for you and patients in general. The findings from this research may be presented at scientific meetings and in journals. In these tables and graphs no individual patient can be identified. We would like to obtain your consent for your data to be used in this way.

We would also like to inform you that your blood samples are stored as part of your routine care. It might be important in the future to look back to see if you carried resistant virus, for example. Occasionally stored samples will be used to train laboratory staff when new types of tests are introduced. Your blood will not be tested for any reason other than for your clinical care without specific consent being obtained from you. If you wish to withdraw consent at any time this will not prejudice your care in any way.

CONSENT FOR USE OF CLINICAL INFORMATION FOR RESEARCH AND DEVELOPMENT

I have read the Patient Information" Request for consent for use of clinical information for research and development" above. I agree that information collected as part of my clinical care can be used for research purposes in the way described on this sheet. I understand that samples of my blood are stored for possible use as part of my own care and that they will not be used for any other purpose without my permission.

Consent refused (tick if applicable) ☐

Patient Name:	
Patient signature:	
Date:	
Name of person seeking consent:	

Request for additional consent:

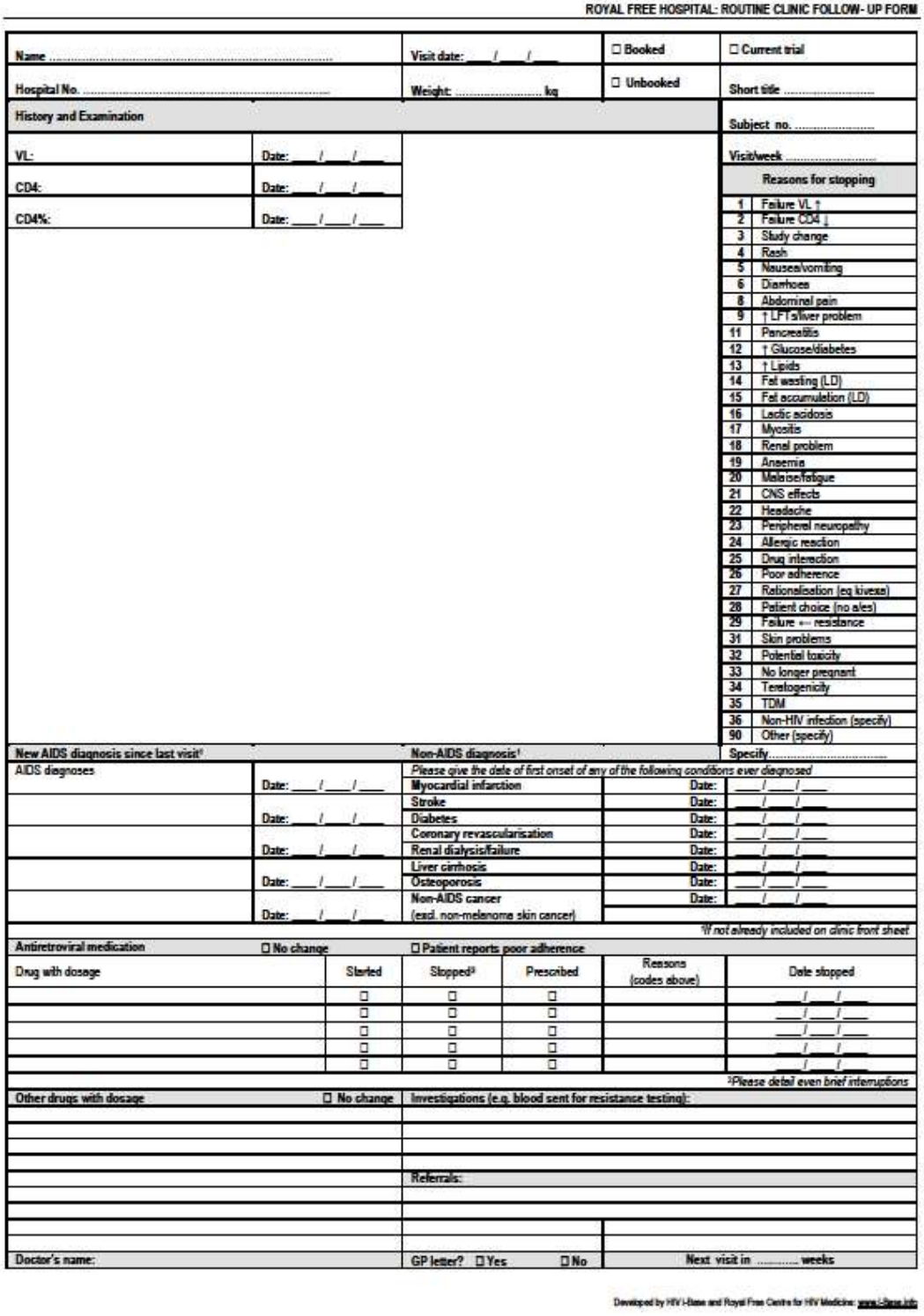
CONSENT FOR GP TO BE CONTACTED

Patient signature ..... **Consent refused (tick if applicable) ☐**

CONSENT FOR LAST HIV/AIDS CARE CENTRE TO BE CONTACTED

Patient signature ..... **Consent refused (tick if applicable) ☐**

Appendix II. Routine clinic follow-up form at the Royal Free Hospital



ROYAL FREE HOSPITAL: ROUTINE CLINIC FOLLOW- UP FORM

Name	Visit date: ___/___/___	☐ Booked	☐ Current trial
Hospital No.	Weight: ..... kg	☐ Unbooked	Short title .....
History and Examination			Subject no. .....
VL:	Date: ___/___/___		Visit/week .....
CD4:	Date: ___/___/___		
CD4%:	Date: ___/___/___		

	Reasons for stopping
1	Failure VL ↑
2	Failure CD4 ↓
3	Study change
4	Rash
5	Nausea/vomiting
6	Diarrhoea
8	Abdominal pain
9	↑ LFTs/liver problem
11	Pancreatitis
12	↑ Glucose/diabetes
13	↑ Lipids
14	Fat wasting (LD)
15	Fat accumulation (LD)
16	Lactic acidosis
17	Myositis
18	Renal problem
19	Anaemia
20	Malaise/fatigue
21	CNS effects
22	Headache
23	Peripheral neuropathy
24	Allergic reaction
25	Drug interaction
26	Poor adherence
27	Rationalisation (eg kivexa)
28	Patient choice (no a/es)
29	Failure +/- resistance
31	Skin problems
32	Potential toxicity
33	No longer pregnant
34	Teratogenicity
35	TDM
36	Non-HIV infection (specify)
90	Other (specify)

Specify.....

New AIDS diagnosis since last visit[1]		Non-AIDS diagnosis[1]		
AIDS diagnoses	Date: ___/___/___	*Please give the date of first onset of any of the following conditions ever diagnosed*		
		Myocardial infarction	Date:	___/___/___
	Date: ___/___/___	Stroke	Date:	___/___/___
		Diabetes	Date:	___/___/___
	Date: ___/___/___	Coronary revascularisation	Date:	___/___/___
		Renal dialysis/failure	Date:	___/___/___
	Date: ___/___/___	Liver cirrhosis	Date:	___/___/___
		Osteoporosis	Date:	___/___/___
	Date: ___/___/___	Non-AIDS cancer (excl. non-melanoma skin cancer)	Date:	___/___/___

[1]If not already included on clinic front sheet

Antiretroviral medication ☐ No change			☐ Patient reports poor adherence			
Drug with dosage		Started	Stopped[2]	Prescribed	Reasons (codes above)	Date stopped
		☐	☐	☐		___/___/___
		☐	☐	☐		___/___/___
		☐	☐	☐		___/___/___
		☐	☐	☐		___/___/___
		☐	☐	☐		___/___/___

[2]Please detail even brief interruptions

Other drugs with dosage ☐ No change	Investigations (e.g. blood sent for resistance testing):	
	Referrals:	
Doctor's name:	GP letter? ☐ Yes ☐ No	Next visit in ..... weeks

Developed by HIV i-Base and Royal Free Centre for HIV Medicine: www.i-Base.info

Appendix III. ASTRA questionnaire information sheet

ASTRA INFORMATION SHEET

Version 2.1 01/08/2011

This information sheet and the other study documents are also available in French. Just ask the clinic nurse if you would prefer a French copy.

ASTRA Questionnaire Study

We would like to invite you to take part in a research study. Please take some time to read this information about the study and decide whether or not to take part. Please ask the person who invited you to take part if anything is unclear or if you have any other questions.

What is the study about?

This is a questionnaire study, looking at how HIV and HIV treatment (antiretroviral treatment) affects people's lives, including their health, quality of life, and lifestyle. In particular, the study will investigate the link between HIV treatment and sexual lifestyles. The results will be used to help decide what the effects would be of offering immediate treatment to all people in the UK who are diagnosed with HIV.

Who is taking part?

This study is being conducted at five HIV clinics in the UK. Everyone coming to each of these clinics is eligible to take part. This includes people who are not taking HIV treatment as well as those who are on treatment. We would like as many people as possible to participate, and so your contribution is important.

What will I have to do?

If you agree to take part, you will be asked to complete a questionnaire about your health and well-being, your lifestyle, your experience of having HIV, and your views on HIV treatment. The questionnaire includes some personal questions about your sex life. You can complete the questionnaire on your own. It should take 15 to 30 minutes to complete.

When will I complete the questionnaire?

We would like you to complete the questionnaire today, while you are here in the clinic, either before or after seeing the doctor. There is a private space available for you to complete your questionnaire, if you would prefer this. The study nurse will make sure you don't miss your appointment with the doctor. If you would like to take part in the study but are unable to complete the questionnaire here in the clinic, you may take it away to complete, and post it back directly to the study centre in the pre-paid envelope. If you do decide to take the questionnaire away, the study nurse will ask if you agree to give a contact number (text or phone) or email which we would use to send a single reminder to you in the event that your questionnaire was not received back at the study centre in due course. This reminder would not mention HIV.

Will my questionnaire responses be confidential?

Yes, completely. Your name or clinic number will NOT be written on the questionnaire. Your answers will NOT be seen by the doctors and nurses in the clinic, and your answers will NEVER be recorded in your clinic notes. Your completed questionnaire can be placed in a sealed envelope which will not be opened by the clinic staff.

What clinical information will be recorded?

If you agree to take part in the study, we will record your latest viral load and CD4 count as part of the study data.

Will any other information about me be gathered?

You will be asked if you agree to us adding your routine HIV clinical information (from this clinic only) to the questionnaire information. This is so we can see how peoples' questionnaire responses relate to their current and future situation. The HIV clinical information would be:

- Your laboratory test results (e.g. viral load and CD4 count)
- Your HIV treatment details
- Other routine information on your HIV care (e.g. any illnesses or hospital admissions)

This is a standard procedure for research studies. The clinical information is added in such a way that your questionnaire responses remain completely confidential, and are NEVER put together with your name or clinic number. You do not have to agree to this, and you can still participate in the study if you do not agree. If you do agree, the clinical information will be collected once when everyone has completed the questionnaire, and on several more occasions over the next few years.

What will happen to the information?

Your anonymised responses will be added to everyone else's responses, and analysed by computer. The data will only be analysed for groups and not for individuals. The findings will be submitted to medical journals and national and international health conferences. Details of publications from this study will be made available on the ASTRA study website (www.astra-study.org).

Do I have to take part?

It is up to you to decide whether or not to take part. If you do decide to take part you may keep this information sheet and you will be asked to sign the consent form. If you agree to take part you can still change your mind and decide not to complete and submit the questionnaire. If you choose not to take part in the study, this will not affect the standard of care you receive.

Are there any risks in taking part?

There is no risk to you in taking part in the study. If you find the questionnaire raises issues that concern you, or that you would like to discuss further, please ask the nurse to arrange for you to speak to *[insert appropriate clinic/local health professional*.....

Who is leading this research?

A team of HIV specialists and researchers from the UK is leading this study. The study is being coordinated by the Research Department of Infection and Population Health, University College London, and is funded by the National Institute for Health Research (NIHR). This study has been reviewed and approved by a research ethics committee.

Site lead .....
Site.....

Dr Fiona Lampe
Research Department of Infection and Population Health, University College London.

Appendix IV. ASTRA questionnaire consent form

CONSENT FORM for ASTRA Questionnaire Study
Version 2.1a 19/06/2012

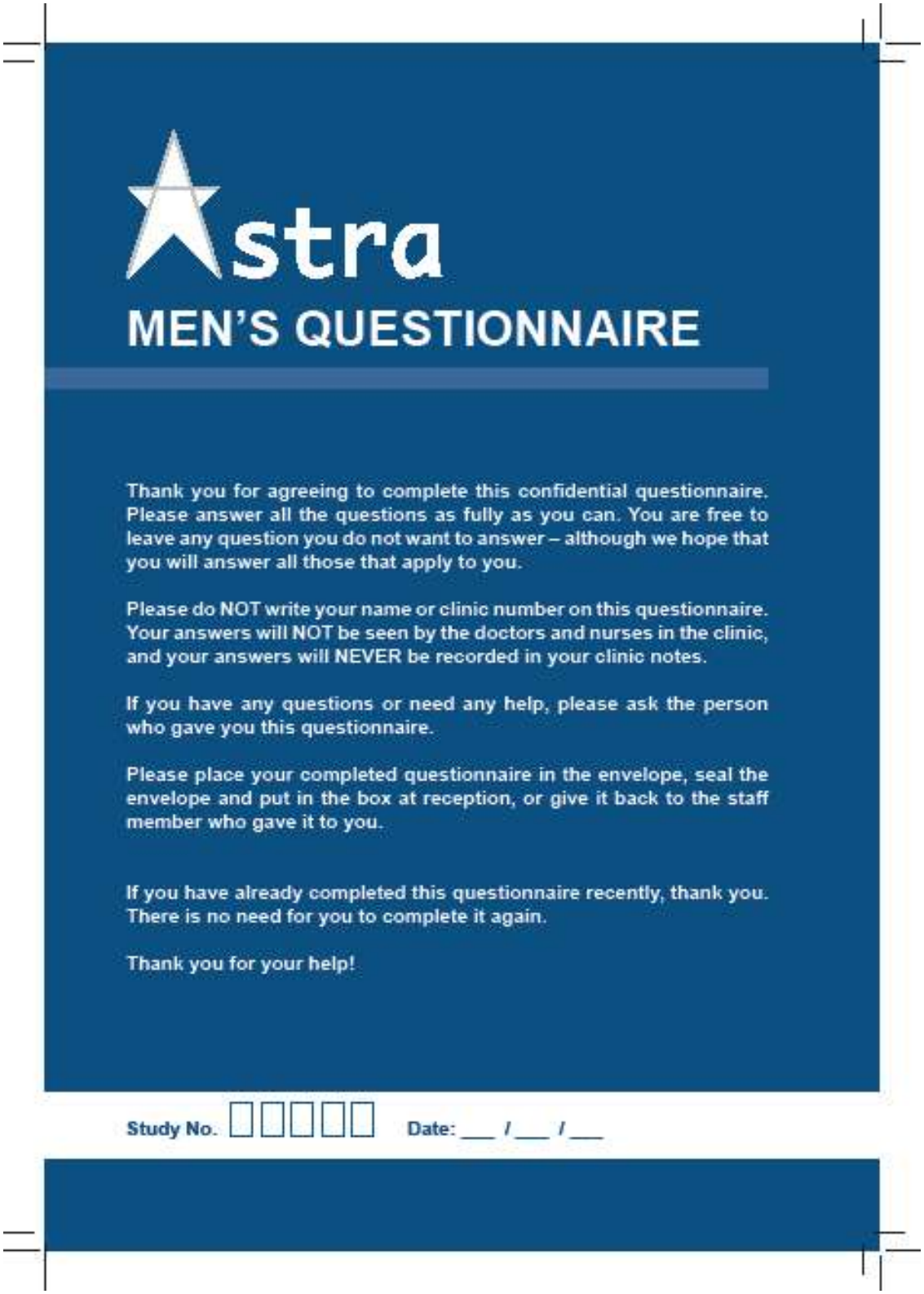
Clinical centre: .....
ASTRA Study ID: _____
Clinic Number: _____

1. I confirm that I have read and understand the information sheet (version 2.1, dated 01/08/2011) for this study. I have had the opportunity to consider the information, ask questions, and have had these answered satisfactorily.	☐ Please initial box
2. I agree to take part in this study.	☐ Please initial box
3. I understand that my participation is voluntary and that I am free to withdraw at any time, without giving any reason, without my medical care or legal rights being affected.	☐ Please initial box
4. I agree / do not agree that information from this clinic on my laboratory test results, HIV treatment and clinical care can be added to my questionnaire responses.	Please initial one box only ☐ YES, I agree ☐ NO, I do not agree

_____	__ __/__ __/__ __ __ __	_____
Name of patient	Date	Signature
_____	__ __/__ __/__ __ __ __	_____
Name of person taking consent	Date	Signature

When completed: 1 for participant; 1 for researcher site file; 1 (original) to be kept in medical notes

Appendix V. ASTRA questionnaire – version for men



Astra

MEN'S QUESTIONNAIRE

Thank you for agreeing to complete this confidential questionnaire. Please answer all the questions as fully as you can. You are free to leave any question you do not want to answer – although we hope that you will answer all those that apply to you.

Please do NOT write your name or clinic number on this questionnaire. Your answers will NOT be seen by the doctors and nurses in the clinic, and your answers will NEVER be recorded in your clinic notes.

If you have any questions or need any help, please ask the person who gave you this questionnaire.

Please place your completed questionnaire in the envelope, seal the envelope and put in the box at reception, or give it back to the staff member who gave it to you.

If you have already completed this questionnaire recently, thank you. There is no need for you to complete it again.

Thank you for your help!

Study No. ☐☐☐☐☐ Date: ___ / ___ / ___

SECTION A: GENERAL INFORMATION

A1. What is your date of birth? Month: __ __ __ Year: __ __ __ __

A2. Which ethnic group best describes you? (Please tick ONE ONLY)

A. White
- ☐ White British
- ☐ White Irish
- ☐ White other

B. Black or Black British
- ☐ Black African
- ☐ Black Caribbean
- ☐ Black other

C. Asian or Asian British
- ☐ Indian
- ☐ Pakistani
- ☐ Bangladeshi
- ☐ Asian other

D. Mixed
- ☐ White and Black African
- ☐ White and Black Caribbean
- ☐ White and Asian
- ☐ Mixed other

E. Chinese or other ethnic group
- ☐ Chinese
- ☐ Any other ethnic group

A3. Were you born in the UK?

☐ **Yes → PLEASE GO TO QUESTION A4**
☐ **No**

If NO, which country were you born in?.....

When did you first move to the UK?
- ☐ Less than 1 year ago
- ☐ 1 to 5 years ago
- ☐ More than 5 years ago

How well do you speak English?
- ☐ Very well / fluent
- ☐ Quite well
- ☐ Not at all well

How well can you read English?
- ☐ Very well / fluent
- ☐ Quite well
- ☐ Not at all well

A4. What is your current work situation? (Please tick ONE ONLY)

- ☐ Employed or self-employed FULL-TIME (at least 30 hours per week)
- ☐ Employed or self-employed PART-TIME (less than 30 hours per week)
- ☐ Full time student / education / training
- ☐ Unemployed and registered for benefits
- ☐ Unemployed, NOT registered for benefits
- ☐ Permanently sick / disabled (for 3 months or more)
- ☐ Temporarily sick / disabled (for less than 3 months)
- ☐ Looking after home / family / dependants full-time
- ☐ Retired
- ☐ Other (please specify)……

A5. What is your current housing situation?

- ☐ Own my own home (including with mortgage / loan / shared ownership)
- ☐ Renting from the council or housing association
- ☐ Renting from private landlord
- ☐ Temporary accommodation (hostel, shelter, bed & breakfast, squat)
- ☐ Staying with partner / friend(s) / family
- ☐ Homeless
- ☐ Other (please specify)……

A6. Do you have enough money to cover your basic needs?
(e.g. food, heating)

- ☐ Yes, all of the time
- ☐ Yes, most of the time
- ☐ Yes, some of the time
- ☐ No

A7. At what level did you COMPLETE your education?
(Please tick ONE ONLY)

- ☐ Finished education with no qualifications
- ☐ O levels / GCSEs (or equivalent qualifications at age 16)
- ☐ A levels (or equivalent qualifications at age 18)
- ☐ University degree or above
- ☐ Other qualifications (please specify)……

A8. Do you regard yourself as belonging to any particular religion?

- ☐ No religion
- ☐ Islam / Muslim
- ☐ Christianity
- ☐ Judaism
- ☐ Hinduism
- ☐ Buddhism
- ☐ Sikhism
- ☐ Other (please specify).....

If YES, do you regularly (at least once a month) **attend religious meetings?** (not including weddings and funerals)

☐ Yes ☐ No

A9. How would you describe your sexuality?

- ☐ Gay / homosexual
- ☐ Straight / heterosexual
- ☐ Bisexual
- ☐ Other (please specify).....

A10. Are you currently in an ongoing relationship with a partner (wife / husband or civil partner or girlfriend / boyfriend)?

- ☐ Yes, I am in a relationship and living with my partner
- ☐ Yes, I am in a relationship but not living with my partner
- ☐ No, I am not currently in an ongoing relationship with a partner

If YES overall, how long have you been in this relationship?

__ __ months __ __ years

Does your partner have HIV? ☐ Yes ☐ No ☐ Don't know

A11. Do you have any children?

- ☐ Yes
- ☐ No

A12. What is your immigration status in the UK? This information is completely confidential and WILL NOT be released to any other organisation. (Please tick one only)

- ☐ I am a British citizen
- ☐ I am a citizen of another EU (European Union) country
- ☐ I have a right to stay for an indefinite amount of time (Indefinite Leave to Remain – ILR)
- ☐ I have a right to stay for a fixed amount of time (Exceptional Leave to Remain – ELR)
- ☐ I am a refugee seeking asylum
- ☐ I have a student visa
- ☐ I have a work permit
- ☐ I have no papers to be in the UK
- ☐ Other (please specify).....

SECTION B: YOU AND HIV

B1. When did you first find out you were HIV positive?
If you are unsure of the month, please give the year only

Month: ___ ___ Year: ___ ___ ___ ___

B2. How long have you been attending this HIV clinic?

☐ Less than 1 year ☐ 1 to 3 years ☐ 3 years or longer

B3. What is the most likely way that you became infected with HIV? Choose the most likely way, even if you are uncertain:

☐ Sex with a man who was HIV positive
☐ Sex with a woman who was HIV positive
☐ Shared needles or other injection equipment with a person who was HIV positive
☐ Blood transfusion, blood products or medical procedure
☐ Needle stick or other exposure while at work (occupational exposure)
☐ Born with HIV infection
☐ Unknown
☐ Other (please specify).....

B4. At your last test what was your CD4 count?

☐ Less than 200
☐ 200-350
☐ 351-500
☐ More than 500
☐ Don't know / can't remember

B5. Apart from health care staff, have you told anyone that you have HIV?

☐ Yes
☐ No → **PLEASE GO TO QUESTION C1**

If YES, who have you told?

I have told a partner / wife / husband	☐ Yes	☐ No	☐ Not applicable
I have told other family members →	☐ None	☐ Some	☐ Most or all
I have told my friends →	☐ None	☐ Some	☐ Most or all
I have told my work colleagues →	☐ None	☐ Some	☐ Most or all
			☐ Not applicable

SECTION C: YOUR HEALTH AND WELLBEING

In this part of the questionnaire, we are using some standard sets of questions to ask you about your health. We apologise if some of the questions seem repetitive, but please take the time to answer each section, as each one is important. Thank you for your help!

If you are worried about any symptoms, please talk to your doctor. The answers from this survey will not be seen by anyone involved in your care.

C1. Below is a list of symptoms. Did you have any of these symptoms during the PAST 2 WEEKS? Please tick one box in each row to tell us whether you have had the symptom and, if so, how much it DISTRESSED or BOTHERED you.

Did you have any of these symptoms during the PAST 2 WEEKS?	No did not have the symptom	Yes, had symptom but it DID NOT BOTHER ME	Yes, had symptom and was bothered / distressed A LITTLE BIT	Yes, had symptom and was bothered / distressed QUITE A BIT	Yes, had symptom and was bothered / distressed VERY MUCH
1. Difficulty concentrating	☐	☐	☐	☐	☐
2. Difficulty sleeping	☐	☐	☐	☐	☐
3. Lack of energy	☐	☐	☐	☐	☐
4. Feeling drowsy / tired	☐	☐	☐	☐	☐
5. Trouble remembering things	☐	☐	☐	☐	☐
6. Pain	☐	☐	☐	☐	☐
7. Headache	☐	☐	☐	☐	☐
8. Numbness, tingling or pain in hands or feet	☐	☐	☐	☐	☐
9. Muscle aches or joint pains	☐	☐	☐	☐	☐
10. Nausea	☐	☐	☐	☐	☐
11. Vomiting	☐	☐	☐	☐	☐
12. Diarrhoea	☐	☐	☐	☐	☐
13. Constipation	☐	☐	☐	☐	☐
14. Feeling bloated	☐	☐	☐	☐	☐
15. Dizziness	☐	☐	☐	☐	☐
16. Sweats / fever	☐	☐	☐	☐	☐
17. Cough	☐	☐	☐	☐	☐
18. Shortness of breath	☐	☐	☐	☐	☐
19. Problems with sexual interest / activity	☐	☐	☐	☐	☐

C1. Continued

Did you have any of these symptoms during the PAST 2 WEEKS? Please tick one box in each row to tell us whether you have had the symptom and, if so, how much it DISTRESSED or BOTHERED you.

Did you have any of these symptoms during the PAST 2 WEEKS?	No did not have the symptom	Yes, had symptom but it DID NOT BOTHER ME	Yes, had symptom and was bothered / distressed A LITTLE BIT	Yes, had symptoms and was bothered / distressed QUITE A BIT	Yes, had symptoms and was bothered / distressed VERY MUCH
20. Skin problems (e.g. rash, itching, dryness)	☐	☐	☐	☐	☐
21. Dry mouth	☐	☐	☐	☐	☐
22. Mouth sores	☐	☐	☐	☐	☐
23. Lack of appetite	☐	☐	☐	☐	☐
24. Changes in way food tastes	☐	☐	☐	☐	☐
25. Weight loss	☐	☐	☐	☐	☐
26. Changes in fat in face or body	☐	☐	☐	☐	☐

C2. Over the PAST 2 WEEKS, how often have you been bothered by any of the following problems? Please tick one box in each row

	Not at all	Several days	More than half the days	Nearly every day
1) Little interest or pleasure in doing things	☐	☐	☐	☐
2) Feeling down, depressed, or hopeless	☐	☐	☐	☐
3) Feeling sad	☐	☐	☐	☐
4) Feeling nervous, anxious or on edge	☐	☐	☐	☐
5) Not being able to stop or control worrying	☐	☐	☐	☐
6) Worrying too much about different things	☐	☐	☐	☐
7) Becoming easily annoyed or irritable	☐	☐	☐	☐
8) Trouble relaxing	☐	☐	☐	☐
9) Being so restless that it is hard to sit still	☐	☐	☐	☐
10) Feeling afraid as if something awful might happen	☐	☐	☐	☐
11) Trouble falling or staying asleep, or sleeping too much	☐	☐	☐	☐
12) Feeling tired or having little energy	☐	☐	☐	☐
13) Poor appetite or overeating	☐	☐	☐	☐
14) Feeling bad about yourself – or that you are a failure or have let yourself or your family down	☐	☐	☐	☐
15) Trouble concentrating on things, such as reading the newspaper or watching television	☐	☐	☐	☐
16) Moving or speaking so slowly that other people could have noticed	☐	☐	☐	☐
17) Thoughts that you would be better off dead, or of hurting yourself in some way	☐	☐	☐	☐
If you were bothered by any of these problems, how difficult have they made it for you to do your work, take care of things at home, or get along with other people?	☐ Not at all difficult ☐ Somewhat difficult ☐ Very difficult ☐ Extremely difficult			

C3. Please indicate which statements best describe your own state of health TODAY. Please tick one box in each section

a) Mobility

- ☐ I have no problems in walking about
- ☐ I have some problems in walking about
- ☐ I am confined to bed

b) Self-care

- ☐ I have no problems with self-care
- ☐ I have some problems washing or dressing myself
- ☐ I am unable to wash or dress myself

c) Usual activities (e.g. work, study, housework, family or leisure activities)

- ☐ I have no problems with performing my usual activities
- ☐ I have some problems with performing my usual activities
- ☐ I am unable to perform my usual activities

d) Pain / discomfort

- ☐ I have no pain or discomfort
- ☐ I have moderate pain or discomfort
- ☐ I have extreme pain or discomfort

e) Anxiety / depression

- ☐ I am not anxious or depressed
- ☐ I am moderately anxious or depressed
- ☐ I am extremely anxious or depressed

C4. Here is a list of some things that other people do for us that may be helpful or supportive. Please read each statement carefully and place a tick in the column that is closest to your situation.
Give only one answer for each row.

	As much as I would like	Almost as much as I would like	Some, but would like more	Less than I would like	Much less than I would like
a) I have people who care what happens to me	☐	☐	☐	☐	☐
b) I get love and affection	☐	☐	☐	☐	☐
c) I get chances to talk to someone I trust about my personal problems	☐	☐	☐	☐	☐
d) I get invitations to go out and do things with other people	☐	☐	☐	☐	☐
e) I get help when I am sick in bed	☐	☐	☐	☐	☐

C5. In the PAST 3 MONTHS, have you been diagnosed with a sexually transmitted infection (not including HIV)?

☐ Yes ☐ No → PLEASE GO TO QUESTION C6

If YES, have you had any of the following in the PAST 3 MONTHS?
Please tick MORE THAN ONE box, if applicable

☐ Syphilis
☐ Gonorrhoea
☐ Chlamydia
☐ LGV
☐ New Hepatitis B
☐ New Hepatitis C
☐ Genital herpes (new or recurrent)
☐ Genital warts (new or recurrent)
☐ Trichomonas
☐ NSU (Non Specific Urethritis), NGU (Non Gonococcal Urethritis)
☐ Other (please specify) .....

C6. Do you currently have any of the following symptoms?
For each symptom, please tick Yes or No

a) Abnormal discharge from penis	☐ Yes	☐ No
b) Anal discharge	☐ Yes	☐ No
c) Pain on passing urine	☐ Yes	☐ No
d) Pain in the genital area or anus	☐ Yes	☐ No
e) Red sores or rash on the genital area or anus	☐ Yes	☐ No

C7. In the PAST 2 YEARS, have you had a sexual health screen (tests for sexually transmitted infections, not including HIV)**?**

☐ Yes ☐ No ☐ Don't know

C8. Have you ever been told by a doctor that you have Hepatitis C?

☐ Yes ☐ No

C9. Are you currently receiving treatment (medicine or other therapy) **for depression?**

☐ Yes ☐ No

C10. Are you currently receiving treatment (medicine or other therapy) **for any other mental health problem?**

☐ Yes (please specify condition).....

☐ No

SECTION D:
YOUR VIEWS ON HIV TRANSMISSION RISK

D1. During the PAST 6 MONTHS, did any of the HIV clinic staff discuss with you condom use and safe sex?
Please tick MORE THAN ONE box, if applicable

- ☐ Yes, discussed with HIV doctor
- ☐ Yes, discussed with HIV nurse
- ☐ Yes, discussed with other clinic staff (e.g. HIV health advisor, HIV counsellor)
- ☐ No, did not discuss with any of the HIV clinic staff
- ☐ Don't remember

D2. Here are some statements about HIV. Please read each statement carefully and place a tick in the box that is closest to your viewpoint.
Give only one answer for each row.

	Strongly agree	Tend to agree	Undecided or no opinion	Tend to disagree	Strongly disagree
a) Better HIV treatment means that people are less worried about catching HIV	☐	☐	☐	☐	☐
b) Better HIV treatment means that people with HIV are less worried about infecting others	☐	☐	☐	☐	☐
c) An undetectable HIV viral load makes someone less infectious to a sexual partner than if they had a high viral load	☐	☐	☐	☐	☐
d) When viral load is undetectable, a condom is not needed to prevent HIV transmission	☐	☐	☐	☐	☐

SECTION E: HIV TREATMENT

E1. Have you ever taken HIV treatment
(antiretroviral treatment / HAART)?

☐ Yes ☐ No → **PLEASE GO TO QUESTION E12**

Questions E2 to E11 are for all patients who are taking or have ever taken HIV treatment

E2. When did you start taking HIV treatment?
If you are unsure of the month, please give the year only

Month: __ __ __ Year: __ __ __ __

E3. Did you start antiretroviral treatment because HIV was making you ill?

☐ Yes ☐ No

E4. Please tick which response is closest to your own view: "Compared to what I expected before starting HIV treatment, taking treatment was..."

☐ Much worse than I expected
☐ A bit worse than I expected
☐ About the same as I expected
☐ A bit better than I expected
☐ Much better than I expected
☐ Don't know / can't remember

E5. When did you get your last viral load test results?

☐ Today
☐ Less than 3 months ago
☐ 3 to 6 months ago
☐ Over 6 months ago
☐ Don't know

E6. What was your viral load the last time you got your test results?

- ☐ 50 copies/mL or less ('undetectable' or 'suppressed')
- ☐ More than 50 copies/mL ('detectable' or 'raised')
- ☐ Don't know

E7. Have you ever changed your HIV treatment because it was not keeping your viral load down?

- ☐ Yes
- ☐ No
- ☐ Don't know

E8. Are you currently taking HIV treatment?

- ☐ Yes → **PLEASE GO TO QUESTION E9**
- ☐ No

If NO:

When did you stop taking treatment?

- ☐ Less than 1 month ago
- ☐ 1 to 6 months ago
- ☐ More than 6 months ago

Why did you stop taking treatment? Please tick all that apply

- ☐ I took HIV treatment only as part of a clinical trial
- ☐ My HIV doctor advised me to stop taking treatment
- ☐ I stopped because of treatment side effects
- ☐ I stopped because I wanted a break from treatment
- ☐ I stopped because treatment was not working
- ☐ I found it difficult to take regular treatment
- ☐ Other (please specify).....

If you are no longer taking HIV treatment please go to question F1

E9. How often do you need to take your HIV treatment?

- ☐ Once a day
- ☐ Twice a day
- ☐ Other (please specify).....

E10. In the LAST 2 WEEKS, how many doses of HIV treatment have you missed?
Once a day treatment = 14 doses in 2 weeks
Twice a day treatment = 28 doses in 2 weeks

- ☐ Missed no doses in last 2 weeks (took all treatment)
- ☐ Missed 1 dose
- ☐ Missed 2 doses
- ☐ Missed 3 doses
- ☐ Missed 4 to 6 doses
- ☐ Missed 7 to 9 doses
- ☐ Missed 10 or more doses (please give approximate number missed……)

If you missed at least one dose in the LAST 2 WEEKS, what were the reasons for this? For each reason please tick Yes or No

a) Treatment was making me feel ill	☐ Yes	☐ No
b) I forgot to take pills	☐ Yes	☐ No
c) I was away from home and forgot to bring my pills	☐ Yes	☐ No
d) I ran out of pills	☐ Yes	☐ No
e) I was in a public place	☐ Yes	☐ No
f) I was with people who did not know I had HIV	☐ Yes	☐ No
g) I was fed up with taking pills	☐ Yes	☐ No
h) I was feeling depressed / low	☐ Yes	☐ No
i) Other (please specify)……	☐ Yes	☐ No

E11. In the PAST 3 MONTHS, have you ever missed your HIV treatment for two or more days at a time?

☐ Yes ☐ No ☐ Don't know / can't remember

If YES, on how many occasions in the past 3 months has this happened?

☐ Once ☐ 2 or 3 times ☐ More than 3 times

PLEASE GO TO QUESTION F1

Questions E12 and E13 are only for patients who have never taken HIV treatment

E12. Here are some statements about starting HIV treatment. Please read each statement carefully and place a tick in the box that is closest to your viewpoint. Give only one answer for each row.

	Strongly agree	Tend to agree	Undecided or no opinion	Tend to disagree	Strongly disagree
a) I would prefer to delay starting HIV treatment for as long as possible, even if this meant a small increased risk of getting a serious illness.	☐	☐	☐	☐	☐
b) I would want to start HIV treatment now, if this would slightly reduce my risk of getting a serious illness.	☐	☐	☐	☐	☐
c) I would want to start HIV treatment now, if this would make me less infectious to a sexual partner (even if there was no benefit to my own health).	☐	☐	☐	☐	☐

E13. Has your HIV doctor ever advised you to start HIV treatment?

☐ Yes ☐ No

If YES, please indicate the main reasons for not starting treatment:
For each reason please tick Yes or No

a) I was worried about the side effects of treatment	☐ Yes	☐ No
b) I was worried about others knowing I had HIV	☐ Yes	☐ No
c) I was worried about developing resistance to treatment	☐ Yes	☐ No
d) I didn't want to take regular medication	☐ Yes	☐ No
e) I wanted to delay starting treatment that I would have to take for the rest of my life	☐ Yes	☐ No
f) I felt well and didn't see the need for treatment	☐ Yes	☐ No
g) I didn't think treatment would help me	☐ Yes	☐ No
h) I would rather let HIV take its natural course	☐ Yes	☐ No
i) Other (please specify).....	☐ Yes	☐ No

SECTION F: LIFESTYLE

F1. Do you smoke cigarettes regularly (at least 1 per day)?

- ☐ Yes → (please give approximate number smoked per day .....)
- ☐ No – I am an ex-smoker (given up smoking)
- ☐ No – I have never smoked

F2. How often do you have a drink that contains alcohol?

- ☐ Never → **PLEASE GO TO QUESTION F8**
- ☐ Monthly or less
- ☐ 2 to 4 times a month
- ☐ 2 to 3 times a week
- ☐ 4 or more times a week

F3. How many units of alcohol* do you drink on a typical day when you are drinking?
*One unit=HALF a pint of beer / cider or a SMALL glass of wine or a SINGLE measure of spirits

☐ 1 or 2 ☐ 3 or 4 ☐ 5 or 6 ☐ 7 to 9 ☐ 10 or more

F4. Have you ever felt you should cut down on your drinking?

☐ Yes ☐ No

F5. Have people annoyed you by criticising your drinking?

☐ Yes ☐ No

F6. Have you ever felt bad or guilty about your drinking?

☐ Yes ☐ No

F7. Have you ever had a drink first thing in the morning to steady your nerves or get rid of a hangover?

☐ Yes ☐ No

F8. In the PAST 3 MONTHS, have you used recreational drugs?
(e.g. poppers, cannabis, cocaine)

☐ Yes ☐ No

If YES, which drugs have you used?
(Please tick MORE THAN ONE box, if applicable)

☐ Acid / LSD / magic mushrooms
☐ Anabolic steroids
☐ Cannabis (marijuana, grass)
☐ Cocaine (coke)
☐ Crack
☐ Codeine
☐ Crystal meth (methamphetamine)
☐ Ecstasy (E)
☐ GHB (liquid ecstasy)
☐ Heroin
☐ Ketamine (K)
☐ Khat (chat)
☐ Mephedrone
☐ Morphine
☐ Opium
☐ Poppers (amyl nitrate)
☐ Speed (amphetamine)
☐ Viagra
☐ Other (please specify)
.....

F9. In the past 3 months, have you injected recreational drugs
(e.g. heroin, crystal meth)?

☐ Yes ☐ No

If YES, after you injected yourself, did you share needles, syringes or 'works' with anyone who did not have HIV or whose HIV-status you didn't know?

☐ Yes ☐ No

SECTION G: SEXUAL LIFESTYLE (MEN)

This section asks about your recent sex life. Remember this information is completely confidential. Your name or clinic number is NOT written on this questionnaire and your answers will NEVER be seen by the clinic staff.

SEX WITH WOMEN

The questions ask about **vaginal sex** and **anal sex.** 'Vaginal sex' means a man's penis in a woman's vagina. 'Anal sex' means a man's penis in a partner's anus (rectum or back passage). 'Sex' means vaginal or anal sex.

G1. In the past 3 months, have you had sex (vaginal or anal sex) **with a woman?**

☐ Yes ☐ No → **PLEASE GO TO QUESTION G6**

If YES, how many women have you had sex with in the past 3 months?

☐ 1 woman - my long-term partner
☐ 1 woman - NOT long-term partner
☐ More than 1 woman (please give approximate number _____)

→ **Was one of these women your long-term partner?**

☐ Yes ☐ No ☐ I don't have a long-term partner

G2. In the past 3 months, have you ever used a condom when you had sex (vaginal or anal sex) **with a woman?**

☐ Yes ☐ No

G3. In the past 3 months, have you had sex (vaginal or anal sex) **with a woman without a condom?**

☐ Yes ☐ No → **PLEASE GO TO QUESTION G6**

G4. In the past 3 months, have you had sex (vaginal or anal sex) **without a condom, with a woman who you knew also had HIV?**

☐ Yes ☐ No → **PLEASE GO TO QUESTION G5**

IF YES: How many HIV-positive women have you had sex with, without a condom in the past 3 months?

☐ 1 woman - my long-term partner
☐ 1 woman - NOT long-term partner
☐ More than 1 woman (please give approximate number _____)

→ **Was one of these women your long-term partner?**

☐ Yes ☐ No ☐ I don't have a long-term partner

G5. In the past 3 months, have you had sex (vaginal or anal sex) **without a condom with a woman who did not have HIV or whose HIV-status you didn't know**

☐ Yes ☐ No → **PLEASE GO TO QUESTION G6**

IF YES:

(i) In the past 3 months, how many women did you have sex (vaginal or anal sex) **with, without a condom? Count only women who did not have HIV, or whose HIV-status you didn't know.**

☐ 1 woman - my long-term partner
☐ 1 woman - NOT long-term partner
☐ More than 1 woman (please give approximate number _____)

→ **Was one of these women your long-term partner?**

☐ Yes ☐ No ☐ I don't have a long-term partner

(ii) In the past 3 months, overall, how many times did you have sex (vaginal or anal sex) **without a condom? Count only times you had sex with women who did not have HIV, or whose HIV-status you didn't know.**

☐ Once
☐ 2 to 10 times
☐ 11 to 30 times
☐ More than 30 times (please give approximate number _____)

(iii) In the past 3 months, did you have anal sex without a condom? Count only anal sex with women who did not have HIV, or whose HIV-status you didn't know.

☐ Yes, at least once ☐ No, never

(iv) In the past 3 months, when you had sex (vaginal or anal sex) **without a condom, did you ejaculate (come) inside your partner? Count only sex with women who did not have HIV, or whose HIV-status you didn't know.**

☐ Yes – some or all of the times
☐ No – none of the times

(v) The last time you had sex (vaginal or anal sex) **without a condom, what were the reasons for not using a condom? This is for sex with a woman who did not have HIV or whose HIV-status you didn't know.**

For each reason please tick Yes or No

a) Trying for pregnancy	☐ Yes	☐ No
b) I believe the risk of HIV transmission is very low	☐ Yes	☐ No
c) Didn't think about using a condom	☐ Yes	☐ No
d) Don't like using condoms	☐ Yes	☐ No
e) My partner didn't want to use a condom	☐ Yes	☐ No
f) Felt unable to discuss condom use	☐ Yes	☐ No
g) Did not have a condom	☐ Yes	☐ No
h) It's more enjoyable / close without a condom	☐ Yes	☐ No
i) Got carried away	☐ Yes	☐ No
j) Under the influence of alcohol or drugs	☐ Yes	☐ No
k) Difficult to keep erection or ejaculate using a condom	☐ Yes	☐ No
l) Feel relaxed about having unprotected sex	☐ Yes	☐ No
m) Other, please specify	☐ Yes	☐ No

SEX WITH MEN

These questions ask about **anal sex** - this means your penis in a partner's anus (rectum or back passage), OR a partner's penis in your anus

G6. In the past 3 months, have you had anal sex with a man?

☐ Yes ☐ No → **PLEASE GO TO QUESTION J1**

If YES, how many men have you had anal sex with in the past 3 months?

☐ 1 man - my long-term partner
☐ 1 man - NOT long-term partner
☐ More than 1 man (please give approximate number _____)

→ **Was one of these men your long-term partner?**

☐ Yes ☐ No ☐ I don't have a long-term partner

G7. In the past 3 months, have you ever used a condom when you had anal sex with a man?

☐ Yes ☐ No

G8. In the past 3 months, have you had anal sex with a man, without a condom?

☐ Yes ☐ No → **PLEASE GO TO QUESTION J1**

G9. In the past 3 months, have you had anal sex without a condom, with a man you knew also had HIV?

☐ Yes ☐ No → **PLEASE GO TO QUESTION G10**

If YES, how many HIV-positive men have you had sex with, without a condom in the past 3 months?

☐ 1 man - my long-term partner
☐ 1 man - NOT long-term partner
☐ More than 1 man (please give approximate number _____)

→ **Was one of these men your long-term partner?**

☐ Yes ☐ No ☐ I don't have a long-term partner

G10. In the past 3 months, have you had anal sex without a condom with a man who did not have HIV or whose HIV-status you didn't know?

☐ Yes ☐ No → PLEASE GO TO QUESTION J1

If YES:

(i) In the past 3 months, how many men did you have anal sex with, without a condom? Count only men who did not have HIV, or whose HIV-status you didn't know.

☐ 1 man - my long-term partner
☐ 1 man - NOT long-term partner
☐ More than 1 man (please give approximate number _____)

→ **Was one of these men your long-term partner?**

☐ Yes ☐ No ☐ I don't have a long-term partner

(ii) In the past 3 months, overall, how many times did you have anal sex without a condom? Count only times you had sex with men who did not have HIV, or whose HIV-status you didn't know.

☐ Once
☐ 2 to 10 times
☐ 11 to 30 times
☐ More than 30 times (please give approximate number _____)

(iii) In the past 3 months, when you had anal sex without a condom, which partner were you? Count only sex with men who did not have HIV, or whose HIV-status you didn't know.

☐ Always the insertive partner (your penis was inside your partner)
☐ Always the receptive partner (your partner's penis was inside you)
☐ Sometimes the insertive partner and sometimes the receptive partner

(iv) In the past 3 months, when you had anal sex without a condom, did you ejaculate (come) inside your partner? Count only sex with men who did not have HIV, or whose HIV-status you didn't know.

☐ Yes – some or all of the times
☐ No – none of the times

(v) The last time you had anal sex without a condom, what were the reasons for not using a condom? This is for sex with a man who did not have HIV or whose HIV-status you didn't know.

For each reason please tick Yes or No

a) I believe the risk of HIV transmission is very low	☐ Yes	☐ No
b) Didn't think about using a condom	☐ Yes	☐ No
c) Don't like using condoms	☐ Yes	☐ No
d) My partner didn't want to use a condom	☐ Yes	☐ No
e) Felt unable to discuss condom use	☐ Yes	☐ No
f) Did not have a condom	☐ Yes	☐ No
g) It's more enjoyable / close without a condom	☐ Yes	☐ No
h) Got carried away	☐ Yes	☐ No
i) Under the influence of alcohol or drugs	☐ Yes	☐ No
j) Difficult for me / partner to keep erection or ejaculate when using a condom	☐ Yes	☐ No
k) Feel relaxed about having unprotected sex	☐ Yes	☐ No
l) Other, please specify	☐ Yes	☐ No

SECTION J: SEXUAL LIFESTYLE (GENERAL)

J1. How much do you agree / disagree with the following statements? Please give only one answer per row.

	Strongly agree	Tend to agree	Undecided / no opinion / not relevant to me	Tend to disagree	Strongly disagree
a) I feel confident that, if I want to, I can make sure a condom is used when I have sex with any partner, in any situation	☐	☐	☐	☐	☐
b) I'd expect to ask a new partner their HIV status before we have sex	☐	☐	☐	☐	☐
c) I'd expect to tell a new partner that I'm HIV-positive before we have sex	☐	☐	☐	☐	☐
d) I find it difficult to discuss condom use with a new sexual partner	☐	☐	☐	☐	☐
e) I am less likely to use a condom with a casual partner	☐	☐	☐	☐	☐
f) I am worried that I could have infected someone else with HIV in the past few months	☐	☐	☐	☐	☐

J2. In the past 3 months, have you used the internet to find a sexual partner?

☐ Yes ☐ No

J3. In the past 3 months, have you participated in group sex? (sex with more than one other person on the same occasion)

☐ Yes ☐ No

J4. In the past 3 months, have you received money for having sex?

☐ Yes ☐ No

J5. In the past 3 months, have you received drugs for having sex?

☐ Yes ☐ No

J6. In the past 3 months, if you have had any HIV-negative sexual partners, have any of them taken HIV drugs to reduce the risk of getting HIV?

- ☐ Yes, a partner has taken PrEP (antiretroviral drugs taken before sex)
- ☐ Yes, a partner has taken PEPSE (antiretroviral drugs taken after sex)
- ☐ No or don't know
- ☐ Have not had sex with an HIV-negative partner in past three months

If YES, did you give your antiretroviral drugs to this partner?

☐ Yes ☐ No

J7. Finally we would like to ask about the past 12 MONTHS. In the past 12 months, how many NEW sexual partners have you had? (this means people you have not had sex with before)

- ☐ No new sexual partners in past 12 months
- ☐ One or more new sexual partners in past 12 months → (please give approximate number .....)

Please use this space to raise any issues you want to

Thank you very much for completing this questionnaire.

Please seal the questionnaire in the envelope provided and put it in the box at reception.

If you took the questionnaire away to complete it, please post it back using the pre-paid envelope.

Thank you.

Further information about HIV and AIDS is available from:

THT DIRECT HELPLINE: **0845 122 1200**
From 10am to 10pm Monday to Friday & 12pm to 6pm Saturday & Sunday.
Telephone advice, information and support service about HIV and AIDS information can also be found on the Terence Higgins Trust website at:
http://***www.tht.org.uk***

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Astra

Appendix VI. ASTRA questionnaire – version for women

Astra

WOMEN'S QUESTIONNAIRE

Thank you for agreeing to complete this confidential questionnaire. Please answer all the questions as fully as you can. You are free to leave any question you do not want to answer – although we hope that you will answer all those that apply to you.

Please do NOT write your name or clinic number on this questionnaire. Your answers will NOT be seen by the doctors and nurses in the clinic, and your answers will NEVER be recorded in your clinic notes.

If you have any questions or need any help, please ask the person who gave you this questionnaire.

Please place your completed questionnaire in the envelope, seal the envelope and put in the box at reception, or give it back to the staff member who gave it to you.

If you have already completed this questionnaire recently, thank you. There is no need for you to complete it again.

Thank you for your help!

Study No. ☐☐☐☐☐ Date: ___ / ___ / ___

SECTION A: GENERAL INFORMATION

A1. What is your date of birth? Month: __ __ __ Year: __ __ __ __

A2. Which ethnic group best describes you? (Please tick ONE ONLY)

A. White
- ☐ White British
- ☐ White Irish
- ☐ White other

B. Black or Black British
- ☐ Black African
- ☐ Black Caribbean
- ☐ Black other

C. Asian or Asian British
- ☐ Indian
- ☐ Pakistani
- ☐ Bangladeshi
- ☐ Asian other

D. Mixed
- ☐ White and Black African
- ☐ White and Black Caribbean
- ☐ White and Asian
- ☐ Mixed other

E. Chinese or other ethnic group
- ☐ Chinese
- ☐ Any other ethnic group

A3. Were you born in the UK?

☐ **Yes** → PLEASE GO TO QUESTION A4
☐ **No**

If NO, which country were you born in?.....

When did you first move to the UK?
- ☐ Less than 1 year ago
- ☐ 1 to 5 years ago
- ☐ More than 5 years ago

How well do you speak English?
- ☐ Very well / fluent
- ☐ Quite well
- ☐ Not at all well

How well can you read English?
- ☐ Very well / fluent
- ☐ Quite well
- ☐ Not at all well

A4. What is your current work situation? (Please tick ONE ONLY)

- ☐ Employed or self-employed FULL-TIME (at least 30 hours per week)
- ☐ Employed or self-employed PART-TIME (less than 30 hours per week)
- ☐ Full time student / education / training
- ☐ Unemployed and registered for benefits
- ☐ Unemployed, NOT registered for benefits
- ☐ Permanently sick / disabled (for 3 months or more)
- ☐ Temporarily sick / disabled (for less than 3 months)
- ☐ Looking after home / family / dependants full-time
- ☐ Retired
- ☐ Other (please specify).....

A5. What is your current housing situation?

- ☐ Own my own home (including with mortgage / loan / shared ownership)
- ☐ Renting from the council or housing association
- ☐ Renting from private landlord
- ☐ Temporary accommodation (hostel, shelter, bed & breakfast, squat)
- ☐ Staying with partner / friend(s) / family
- ☐ Homeless
- ☐ Other (please specify).....

A6. Do you have enough money to cover your basic needs?
(e.g. food, heating)

- ☐ Yes, all of the time
- ☐ Yes, most of the time
- ☐ Yes, some of the time
- ☐ No

A7. At what level did you COMPLETE your education?
(Please tick ONE ONLY)

- ☐ Finished education with no qualifications
- ☐ O levels / GCSEs (or equivalent qualifications at age 16)
- ☐ A levels (or equivalent qualifications at age 18)
- ☐ University degree or above
- ☐ Other qualifications (please specify).....

A8. Do you regard yourself as belonging to any particular religion?

- ☐ No religion
- ☐ Islam / Muslim
- ☐ Christianity
- ☐ Judaism
- ☐ Hinduism
- ☐ Buddhism
- ☐ Sikhism
- ☐ Other (please specify)……

If YES, do you regularly (at least once a month) **attend religious meetings?** (not including weddings and funerals)

☐ Yes ☐ No

A9. How would you describe your sexuality?

- ☐ Gay / homosexual
- ☐ Straight / heterosexual
- ☐ Bisexual
- ☐ Other (please specify)……

A10. Are you currently in an ongoing relationship with a partner (wife / husband or civil partner or girlfriend / boyfriend)?

- ☐ Yes, I am in a relationship and living with my partner
- ☐ Yes, I am in a relationship but not living with my partner
- ☐ No, I am not currently in an ongoing relationship with a partner

If YES overall, how long have you been in this relationship?

__ __ months __ __ years

Does your partner have HIV? ☐ Yes ☐ No ☐ Don't know

A11. Do you have any children?

- ☐ Yes
- ☐ No

If YES, please complete the following for each child:

Age of child in years		Has he / she been tested for HIV?		
1	.....	☐ Yes	☐ No	☐ Don't know
2	.....	☐ Yes	☐ No	☐ Don't know
3	.....	☐ Yes	☐ No	☐ Don't know
4	.....	☐ Yes	☐ No	☐ Don't know
5	.....	☐ Yes	☐ No	☐ Don't know

A12. What is your immigration status in the UK? This information is completely confidential and WILL NOT be released to any other organisation. (Please tick one only)

- ☐ I am a British citizen
- ☐ I am a citizen of another EU (European Union) country
- ☐ I have a right to stay for an indefinite amount of time (Indefinite Leave to Remain – ILR)
- ☐ I have a right to stay for a fixed amount of time (Exceptional Leave to Remain – ELR)
- ☐ I am a refugee seeking asylum
- ☐ I have a student visa
- ☐ I have a work permit
- ☐ I have no papers to be in the UK
- ☐ Other (please specify).....

SECTION B: YOU AND HIV

B1. When did you first find out you were HIV positive?
If you are unsure of the month, please give the year only

Month: _ _ _ Year: _ _ _ _

B2. How long have you been attending this HIV clinic?

☐ Less than 1 year ☐ 1 to 3 years ☐ 3 years or longer

B3. What is the most likely way that you became infected with HIV? Choose the most likely way, even if you are uncertain:

☐ Sex with a man who was HIV positive
☐ Sex with a woman who was HIV positive
☐ Shared needles or other injection equipment with a person who was HIV positive
☐ Blood transfusion, blood products or medical procedure
☐ Needle stick or other exposure while at work (occupational exposure)
☐ Born with HIV infection
☐ Unknown
☐ Other (please specify).....

B4. At your last test what was your CD4 count?

☐ Less than 200
☐ 200-350
☐ 351-500
☐ More than 500
☐ Don't know / can't remember

B5. Apart from health care staff, have you told anyone that you have HIV?

☐ Yes
☐ No → **PLEASE GO TO QUESTION C1**

If YES, who have you told?

I have told a partner / wife / husband	☐ Yes	☐ No	☐ Not applicable
I have told other family members →	☐ None	☐ Some	☐ Most or all
I have told my friends →	☐ None	☐ Some	☐ Most or all
I have told my work colleagues →	☐ None	☐ Some	☐ Most or all
			☐ Not applicable

SECTION C: YOUR HEALTH AND WELLBEING

In this part of the questionnaire, we are using some standard sets of questions to ask you about your health. We apologise if some of the questions seem repetitive, but please take the time to answer each section, as each one is important. Thank you for your help!

If you are worried about any symptoms, please talk to your doctor. The answers from this survey will not be seen by anyone involved in your care.

C1. Below is a list of symptoms. Did you have any of these symptoms during the PAST 2 WEEKS? Please tick one box in each row to tell us whether you have had the symptom and, if so, how much it DISTRESSED or BOTHERED you.

Did you have any of these symptoms during the PAST 2 WEEKS?	No did not have the symptom	Yes, had symptom but it DID NOT BOTHER ME	Yes, had symptom and was bothered / distressed A LITTLE BIT	Yes, had symptom and was bothered / distressed QUITE A BIT	Yes, had symptom and was bothered / distressed VERY MUCH
1. Difficulty concentrating	☐	☐	☐	☐	☐
2. Difficulty sleeping	☐	☐	☐	☐	☐
3. Lack of energy	☐	☐	☐	☐	☐
4. Feeling drowsy / tired	☐	☐	☐	☐	☐
5. Trouble remembering things	☐	☐	☐	☐	☐
6. Pain	☐	☐	☐	☐	☐
7. Headache	☐	☐	☐	☐	☐
8. Numbness, tingling or pain in hands or feet	☐	☐	☐	☐	☐
9. Muscle aches or joint pains	☐	☐	☐	☐	☐
10. Nausea	☐	☐	☐	☐	☐
11. Vomiting	☐	☐	☐	☐	☐
12. Diarrhoea	☐	☐	☐	☐	☐
13. Constipation	☐	☐	☐	☐	☐
14. Feeling bloated	☐	☐	☐	☐	☐
15. Dizziness	☐	☐	☐	☐	☐
16. Sweats / fever	☐	☐	☐	☐	☐
17. Cough	☐	☐	☐	☐	☐
18. Shortness of breath	☐	☐	☐	☐	☐
19. Problems with sexual interest / activity	☐	☐	☐	☐	☐

C1. Continued

Did you have any of these symptoms during the PAST 2 WEEKS? Please tick one box in each row to tell us whether you have had the symptom and, if so, how much it DISTRESSED or BOTHERED you.

Did you have any of these symptoms during the PAST 2 WEEKS?	No did not have the symptom	Yes, had symptom but it DID NOT BOTHER ME	Yes, had symptom and was bothered / distressed A LITTLE BIT	Yes, had symptom and was bothered / distressed QUITE A BIT	Yes, had symptom and was bothered / distressed VERY MUCH
20. Skin problems (e.g. rash, itching, dryness)	☐	☐	☐	☐	☐
21. Dry mouth	☐	☐	☐	☐	☐
22. Mouth sores	☐	☐	☐	☐	☐
23. Lack of appetite	☐	☐	☐	☐	☐
24. Changes in way food tastes	☐	☐	☐	☐	☐
25. Weight loss	☐	☐	☐	☐	☐
26. Changes in fat in face or body	☐	☐	☐	☐	☐

C2. Over the PAST 2 WEEKS, how often have you been bothered by any of the following problems? Please tick one box in each row

	Not at all	Several days	More than half the days	Nearly every day
1) Little interest or pleasure in doing things	☐	☐	☐	☐
2) Feeling down, depressed, or hopeless	☐	☐	☐	☐
3) Feeling sad	☐	☐	☐	☐
4) Feeling nervous, anxious or on edge	☐	☐	☐	☐
5) Not being able to stop or control worrying	☐	☐	☐	☐
6) Worrying too much about different things	☐	☐	☐	☐
7) Becoming easily annoyed or irritable	☐	☐	☐	☐
8) Trouble relaxing	☐	☐	☐	☐
9) Being so restless that it is hard to sit still	☐	☐	☐	☐
10) Feeling afraid as if something awful might happen	☐	☐	☐	☐
11) Trouble falling or staying asleep, or sleeping too much	☐	☐	☐	☐
12) Feeling tired or having little energy	☐	☐	☐	☐
13) Poor appetite or overeating	☐	☐	☐	☐
14) Feeling bad about yourself—or that you are a failure or have let yourself or your family down	☐	☐	☐	☐
15) Trouble concentrating on things, such as reading the newspaper or watching television	☐	☐	☐	☐
16) Moving or speaking so slowly that other people could have noticed	☐	☐	☐	☐
17) Thoughts that you would be better off dead, or of hurting yourself in some way	☐	☐	☐	☐
If you were bothered by any of these problems, how difficult have they made it for you to do your work, take care of things at home, or get along with other people?	☐ Not at all difficult ☐ Somewhat difficult ☐ Very difficult ☐ Extremely difficult			

C3. Please indicate which statements best describe your own state of health TODAY. Please tick one box in each section

a) Mobility

- ☐ I have no problems in walking about
- ☐ I have some problems in walking about
- ☐ I am confined to bed

b) Self-care

- ☐ I have no problems with self-care
- ☐ I have some problems washing or dressing myself
- ☐ I am unable to wash or dress myself

c) Usual activities (e.g. work, study, housework, family or leisure activities)

- ☐ I have no problems with performing my usual activities
- ☐ I have some problems with performing my usual activities
- ☐ I am unable to perform my usual activities

d) Pain / discomfort

- ☐ I have no pain or discomfort
- ☐ I have moderate pain or discomfort
- ☐ I have extreme pain or discomfort

e) Anxiety / depression

- ☐ I am not anxious or depressed
- ☐ I am moderately anxious or depressed
- ☐ I am extremely anxious or depressed

C4. Here is a list of some things that other people do for us that may be helpful or supportive. Please read each statement carefully and place a tick in the column that is closest to your situation.
Give only one answer for each row.

	As much as I would like	Almost as much as I would like	Some, but would like more	Less than I would like	Much less than I would like
a) I have people who care what happens to me	☐	☐	☐	☐	☐
b) I get love and affection	☐	☐	☐	☐	☐
c) I get chances to talk to someone I trust about my personal problems	☐	☐	☐	☐	☐
d) I get invitations to go out and do things with other people	☐	☐	☐	☐	☐
e) I get help when I am sick in bed	☐	☐	☐	☐	☐

C5. In the PAST 3 MONTHS, have you been diagnosed with a sexually transmitted infection (not including HIV)?

☐ Yes ☐ No → PLEASE GO TO QUESTION C6

If YES, have you had any of the following in the PAST 3 MONTHS?
Please tick MORE THAN ONE box, if applicable

- ☐ Syphilis
- ☐ Gonorrhoea
- ☐ Chlamydia
- ☐ LGV
- ☐ New Hepatitis B
- ☐ New Hepatitis C
- ☐ Genital herpes (new or recurrent)
- ☐ Genital warts (new or recurrent)
- ☐ Trichomonas
- ☐ NSU (Non Specific Urethritis), NGU (Non Gonococcal Urethritis)
- ☐ Other (please specify).....

C6. Do you currently have any of the following symptoms?
For each symptom, please tick Yes or No.

a) Abnormal discharge from vagina	☐ Yes	☐ No
b) Anal discharge	☐ Yes	☐ No
c) Pain on passing urine	☐ Yes	☐ No
d) Pain in the genital area or anus	☐ Yes	☐ No
e) Red sores or rash on the genital area or anus	☐ Yes	☐ No

C7. In the PAST 2 YEARS, have you had a sexual health screen (tests for sexually transmitted infections, not including HIV)**?**

☐ Yes ☐ No ☐ Don't know

C8. Have you ever been told by a doctor that you have Hepatitis C?

☐ Yes ☐ No

C9. Are you currently receiving treatment (medicine or other therapy) **for depression?**

☐ Yes ☐ No

C10. Are you currently receiving treatment (medicine or other therapy) **for any other mental health problem?**

☐ Yes (please specify condition).....

☐ No

SECTION D:
YOUR VIEWS ON HIV TRANSMISSION RISK

D1. During the PAST 6 MONTHS, did any of the HIV clinic staff discuss with you condom use and safe sex?
Please tick MORE THAN ONE box, if applicable

- ☐ Yes, discussed with HIV doctor
- ☐ Yes, discussed with HIV nurse
- ☐ Yes, discussed with other clinic staff (e.g. HIV health advisor, HIV counsellor)
- ☐ No, did not discuss with any of the HIV clinic staff
- ☐ Don't remember

D2. Here are some statements about HIV. Please read each statement carefully and place a tick in the box that is closest to your viewpoint.
Give only one answer for each row.

	Strongly agree	Tend to agree	Undecided or no opinion	Tend to disagree	Strongly disagree
a) Better HIV treatment means that people are less worried about catching HIV	☐	☐	☐	☐	☐
b) Better HIV treatment means that people with HIV are less worried about infecting others	☐	☐	☐	☐	☐
c) An undetectable HIV viral load makes someone less infectious to a sexual partner than if they had a high viral load	☐	☐	☐	☐	☐
d) When viral load is undetectable, a condom is not needed to prevent HIV transmission	☐	☐	☐	☐	☐

SECTION E: HIV TREATMENT

E1. Have you ever taken HIV treatment
(antiretroviral treatment / HAART)?

☐ Yes ☐ No → **PLEASE GO TO QUESTION E12**

Questions E2 to E11 are for all patients who are taking or have ever taken HIV treatment

E2. When did you start taking HIV treatment?
If you are unsure of the month, please give the year only

Month: _ _ _ Year: _ _ _ _

E3. Did you start antiretroviral treatment because HIV was making you ill?

☐ Yes ☐ No

E4. Please tick which response is closest to your own view: "Compared to what I expected before starting HIV treatment, taking treatment was..."

☐ Much worse than I expected
☐ A bit worse than I expected
☐ About the same as I expected
☐ A bit better than I expected
☐ Much better than I expected
☐ Don't know / can't remember

E5. When did you get your last viral load test results?

☐ Today
☐ Less than 3 months ago
☐ 3 to 6 months ago
☐ Over 6 months ago
☐ Don't know

E6. What was your viral load the last time you got your test results?

- ☐ 50 copies/mL or less ('undetectable' or 'suppressed')
- ☐ More than 50 copies/mL ('detectable' or 'raised')
- ☐ Don't know

E7. Have you ever changed your HIV treatment because it was not keeping your viral load down?

- ☐ Yes
- ☐ No
- ☐ Don't know

E8. Are you currently taking HIV treatment?

- ☐ Yes → **PLEASE GO TO QUESTION E9**
- ☐ No

If NO:

When did you stop taking treatment?

- ☐ Less than 1 month ago
- ☐ 1 to 6 months ago
- ☐ More than 6 months ago

Why did you stop taking treatment? Please tick all that apply

- ☐ I took HIV treatment only because I was pregnant
- ☐ I took HIV treatment only as part of a clinical trial
- ☐ My HIV doctor advised me to stop taking treatment
- ☐ I stopped because of treatment side effects
- ☐ I stopped because I wanted a break from treatment
- ☐ I stopped because treatment was not working
- ☐ I found it difficult to take regular treatment
- ☐ Other (please specify).....

If you are no longer taking HIV treatment please go to question F1

E9. How often do you need to take your HIV treatment?

- ☐ Once a day
- ☐ Twice a day
- ☐ Other (please specify).....

E10. In the LAST 2 WEEKS, how many doses of HIV treatment have you missed?

Once a day treatment = 14 doses in 2 weeks
Twice a day treatment = 28 doses in 2 weeks

- ☐ Missed no doses in last 2 weeks (took all treatment)
- ☐ Missed 1 dose
- ☐ Missed 2 doses
- ☐ Missed 3 doses
- ☐ Missed 4 to 6 doses
- ☐ Missed 7 to 9 doses
- ☐ Missed 10 or more doses (please give approximate number missed……)

If you missed at least one dose in the LAST 2 WEEKS, what were the reasons for this? For each reason please tick Yes or No

a) Treatment was making me feel ill	☐ Yes	☐ No
b) I forgot to take pills	☐ Yes	☐ No
c) I was away from home and forgot to bring my pills	☐ Yes	☐ No
d) I ran out of pills	☐ Yes	☐ No
e) I was in a public place	☐ Yes	☐ No
f) I was with people who did not know I had HIV	☐ Yes	☐ No
g) I was fed up with taking pills	☐ Yes	☐ No
h) I was feeling depressed / low	☐ Yes	☐ No
i) Other (please specify)……	☐ Yes	☐ No

E11. In the PAST 3 MONTHS, have you ever missed your HIV treatment for two or more days at a time?

☐ Yes ☐ No ☐ Don't know / can't remember

If YES, on how many occasions in the past 3 months has this happened?

☐ Once ☐ 2 or 3 times ☐ More than 3 times

PLEASE GO TO QUESTION F1

Questions E12 and E13 are only for patients who have never taken HIV treatment

E12. Here are some statements about starting HIV treatment. Please read each statement carefully and place a tick in the box that is closest to your viewpoint. Give only one answer for each row.

	Strongly agree	Tend to agree	Undecided or no opinion	Tend to disagree	Strongly disagree
a) I would prefer to delay starting HIV treatment for as long as possible, even if this meant a small increased risk of getting a serious illness.	☐	☐	☐	☐	☐
b) I would want to start HIV treatment now, if this would slightly reduce my risk of getting a serious illness.	☐	☐	☐	☐	☐
c) I would want to start HIV treatment now, if this would make me less infectious to a sexual partner (even if there was no benefit to my own health).	☐	☐	☐	☐	☐

E13. Has your HIV doctor ever advised you to start HIV treatment?

☐ Yes ☐ No

If YES, please indicate the main reasons for not starting treatment:
For each reason please tick Yes or No

a) I was worried about the side effects of treatment	☐ Yes	☐ No
b) I was worried about others knowing I had HIV	☐ Yes	☐ No
c) I was worried about developing resistance to treatment	☐ Yes	☐ No
d) I didn't want to take regular medication	☐ Yes	☐ No
e) I wanted to delay starting treatment that I would have to take for the rest of my life	☐ Yes	☐ No
f) I felt well and didn't see the need for treatment	☐ Yes	☐ No
g) I didn't think treatment would help me	☐ Yes	☐ No
h) I would rather let HIV take its natural course	☐ Yes	☐ No
i) Other (please specify).....	☐ Yes	☐ No

SECTION F: LIFESTYLE

F1. Do you smoke cigarettes regularly (at least 1 per day)?

- ☐ Yes → (please give approximate number smoked per day .....)
- ☐ No – I am an ex-smoker (given up smoking)
- ☐ No – I have never smoked

F2. How often do you have a drink that contains alcohol?

- ☐ Never → **PLEASE GO TO QUESTION F8**
- ☐ Monthly or less
- ☐ 2 to 4 times a month
- ☐ 2 to 3 times a week
- ☐ 4 or more times a week

F3. How many units of alcohol* do you drink on a typical day when you are drinking?
*One unit=HALF a pint of beer / cider or a SMALL glass of wine or a SINGLE measure of spirits

☐ 1 or 2 ☐ 3 or 4 ☐ 5 or 6 ☐ 7 to 9 ☐ 10 or more

F4. Have you ever felt you should cut down on your drinking?

☐ Yes ☐ No

F5. Have people annoyed you by criticising your drinking?

☐ Yes ☐ No

F6. Have you ever felt bad or guilty about your drinking?

☐ Yes ☐ No

F7. Have you ever had a drink first thing in the morning to steady your nerves or get rid of a hangover?

☐ Yes ☐ No

F8. In the PAST 3 MONTHS, have you used recreational drugs?
(e.g. poppers, cannabis, cocaine)

☐ Yes ☐ No

If YES, which drugs have you used?
(Please tick MORE THAN ONE box, if applicable)

☐ Acid / LSD / magic mushrooms
☐ Anabolic steroids
☐ Cannabis (marijuana, grass)
☐ Cocaine (coke)
☐ Crack
☐ Codeine
☐ Crystal meth (methamphetamine)
☐ Ecstasy (E)
☐ GHB (liquid ecstasy)
☐ Heroin
☐ Ketamine (K)
☐ Khat (chat)
☐ Mephedrone
☐ Morphine
☐ Opium
☐ Poppers (amyl nitrate)
☐ Speed (amphetamine)
☐ Viagra
☐ Other (please specify)
.....

F9. In the past 3 months, have you injected recreational drugs
(e.g. heroin, crystal meth)?

☐ Yes ☐ No

If YES, after you injected yourself, did you share needles, syringes or 'works' with anyone who did not have HIV or whose HIV-status you didn't know?

☐ Yes ☐ No

SECTION H: SEXUAL LIFESTYLE (WOMEN)

This section asks about your recent sex life. Remember this information is completely confidential. Your name or clinic number is NOT written on this questionnaire and your answers will NEVER be seen by the clinic staff.

The questions ask about **vaginal sex** and **anal sex.** 'Vaginal sex' means a man's penis in a woman's vagina. 'Anal sex' means a man's penis in a woman's anus (rectum or back passage). 'Sex' means vaginal or anal sex.

H1. Are you pregnant?

☐ Yes
☐ No
☐ Not sure

H2. In the past 3 months, have you had sex (vaginal or anal sex) **with a man?**

☐ Yes
☐ No → **PLEASE GO TO QUESTION J1**

If YES, how many men have you had sex with in the past 3 months?

☐ 1 man - my long-term partner
☐ 1 man - NOT long-term partner
☐ More than 1 man (please give approximate number _____)

→ **Was one of these men your long-term partner?**

☐ Yes ☐ No ☐ I don't have a long-term partner

H3. In the past 3 months, have you ever used a condom when you had sex (vaginal or anal sex) **with a man?**

☐ Yes ☐ No

H4. In the past 3 months, have you had sex (vaginal or anal sex) **with a man without a condom?**

☐ Yes ☐ No → **PLEASE GO TO QUESTION J1**

H5. In the past 3 months, have you had sex (vaginal or anal sex) **without a condom, with a man who you knew also had HIV?**

☐ Yes ☐ No → **PLEASE GO TO QUESTION H6**

IF YES: In the past 3 months, how many HIV-positive men have you had sex with, without a condom?

☐ 1 man - my long-term partner
☐ 1 man - NOT long-term partner
☐ More than 1 man (please give approximate number _____)

→ **Was one of these men your long-term partner?**

☐ Yes ☐ No ☐ I don't have a long-term partner

H6. In the past 3 months, have you had sex (vaginal or anal sex) **without a condom with a man who did not have HIV or whose HIV-status you didn't know?**

☐ Yes ☐ No → **PLEASE GO TO QUESTION J1**

IF YES:

(i) In the past 3 months, how many men did you have sex (vaginal or anal sex) **with, without a condom? Count only men who did not have HIV, or whose HIV-status you didn't know.**

☐ 1 man - my long-term partner
☐ 1 man - NOT long-term partner
☐ More than 1 man (please give approximate number _____)

→ **Was one of these men your long-term partner?**

☐ Yes ☐ No ☐ I don't have a long-term partner

(ii) In the past 3 months overall, how many times did you have sex (vaginal or anal sex) **without a condom? Count only times you had sex with men who did not have HIV, or whose HIV-status you didn't know.**

☐ Once
☐ 2 to 10 times
☐ 11 to 30 times
☐ More than 30 times (please give approximate number _____)

(iii) In the past 3 months, did you have anal sex without a condom? Count only sex with men who did not have HIV, or whose HIV-status you didn't know. ☐ Yes, at least once ☐ No, never

(iv) <u>The last time</u> you had sex (vaginal or anal sex) **without a condom, what were the reasons for not using a condom? This is for sex with a man who did not have HIV or whose HIV-status you didn't know.**

For each reason please tick Yes or No

a)	Trying for pregnancy	☐ Yes	☐ No
b)	I believe the risk of HIV transmission is very low	☐ Yes	☐ No
c)	Didn't think about using a condom	☐ Yes	☐ No
d)	Don't like using condoms	☐ Yes	☐ No
e)	My partner didn't want to use a condom	☐ Yes	☐ No
f)	Felt unable to discuss condom use	☐ Yes	☐ No
g)	Did not have a condom	☐ Yes	☐ No
h)	It's more enjoyable / close without a condom	☐ Yes	☐ No
i)	Got carried away	☐ Yes	☐ No
j)	Under the influence of alcohol or drugs	☐ Yes	☐ No
k)	Difficult for partner to keep erection or ejaculate when using a condom	☐ Yes	☐ No
l)	Feel relaxed about having unprotected sex	☐ Yes	☐ No
m)	Other, please specify	☐ Yes	☐ No

SECTION J: SEXUAL LIFESTYLE (GENERAL)

J1. How much do you agree / disagree with the following statements? Please give only one answer per row.

	Strongly agree	Tend to agree	Undecided / no opinion / not relevant to me	Tend to disagree	Strongly disagree
a) I feel confident that, if I want to, I can make sure a condom is used when I have sex with any partner, in any situation	☐	☐	☐	☐	☐
b) I'd expect to ask a new partner their HIV status before we have sex	☐	☐	☐	☐	☐
c) I'd expect to tell a new partner that I'm HIV-positive before we have sex	☐	☐	☐	☐	☐
d) I find it difficult to discuss condom use with a new sexual partner	☐	☐	☐	☐	☐
e) I am less likely to use a condom with a casual partner	☐	☐	☐	☐	☐
f) I am worried that I could have infected someone else with HIV in the past few months	☐	☐	☐	☐	☐

J2. In the past 3 months, have you used the internet to find a sexual partner?

☐ Yes ☐ No

J3. In the past 3 months, have you participated in group sex?
(sex with more than one other person on the same occasion)

☐ Yes ☐ No

J4. In the past 3 months, have you received money for having sex?

☐ Yes ☐ No

J5. In the past 3 months, have you received drugs for having sex?

☐ Yes ☐ No

J6. In the past 3 months, if you have had any HIV-negative sexual partners, have any of them taken HIV drugs to reduce the risk of getting HIV?

- ☐ Yes, a partner has taken PrEP (antiretroviral drugs taken before sex)
- ☐ Yes, a partner has taken PEPSE (antiretroviral drugs taken after sex)
- ☐ No or don't know
- ☐ Have not had sex with an HIV-negative partner in past 3 months

If YES: did you give your antiretroviral drugs to this partner?

☐ Yes ☐ No

J7. Finally we would like to ask about the past 12 MONTHS. In the past 12 months, how many NEW sexual partners have you had?
(this means people you have not had sex with before)

- ☐ No new sexual partners in past 12 months
- ☐ One or more new sexual partners in past 12 months → (please give approximate number .....)

Please use the space on the back cover to raise any issues you want to

Please use this space to raise any issues you want to

Thank you very much for completing this questionnaire.

Please seal the questionnaire in the envelope provided and put it in the box at reception.

If you took the questionnaire away to complete it, please post it back using the pre-paid envelope.

Thank you.

Further information about HIV and AIDS is available from:

THT DIRECT HELPLINE: **0845 122 1200**
From 10am to 10pm Monday to Friday & 12pm to 6pm Saturday & Sunday.
Telephone advice, information and support service about HIV and AIDS information can also be found on the Terence Higgins Trust website at:
http://***www.tht.org.uk***

THIS PROJECT IS RUN BY:
Research Department of Infection and Population Health,
University College London, in collaboration with
Royal Free Hampstead NHS Trust
Mortimer Market Centre, Camden PCT
Homerton Hospital NHS Trust
Brighton and Sussex University Hospitals NHS Trust
North Manchester General Hospital (Pennine Acute Hospitals NHS Trust)

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Astra

Appendix VII. Longitudinal ASTRA data collection guidance

ASTRA Clinical Data Submission: Second Phase

We are now requesting the second delivery of anonymised clinical data from the participating centres as agreed in the original ASTRA study protocol. We would like to receive all data **by Friday 20th December 2013 to coincide with the delivery deadline for UK CHIC.**

Note that we have tried to ensure that the clinical data to be provided is very similar to current UK CHIC requirements. In particular you will see that Tables 2 to 8 are almost identical to UK CHIC - and have been revised to fit with the current CHIC specification - and Table 1 is a subset of the UK CHIC equivalent.

In addition there is another optional data table - Table 9 (Hospital admissions). You only need to provide this if the data are readily available at your site.

Data is to be provided on those patients that participated in ASTRA and gave the additional consent to supply clinical data. A list of ASTRA Study IDs with the correct permissions will be provided and you can match this up to your local Clinic Identifiers using the "Clinical Linkage Consent" worksheet in the "AstraClinicConsent" spreadsheet already provided.

If you have any queries, please contact Andrew Speakman (020 7794 0500 ext. 34680) or email a.speakman@ucl.ac.uk

Thank you.

Data to be collected

General points:

- All data can be provided as access tables, excel spreadsheets or text files with the variables comma or tab delimited
- All dates should be provided in dd/mm/yyyy format, including leading zeros
- All tables should include the ASTRA Study ID and date of birth for each patient so that the files can be easily matched and cross checked. **Note that the date of birth will be used to cross check for validity at the time of data import.**
- DO NOT send patient names, addresses or any other identifiable information.
- We will contact you to arrange a secure method of transferring to our systems when the data are ready.
- Unless otherwise specified, variables in the data tables should be coded using the latest (November 2013) UK CHIC codes. The definitions have been updated including changes (highlighted in blue) to the following tables: ANTIRETRO (DrugID 14, 97, >110), VIRAL LOAD (AssayID 22-31), HEPATITIS (UndetID, HepUnitID) and TOXICITY (ToxTestID 28-31 and ToxUnitID 15-19)
- If there are any problems supplying data in the indicated format, please contact us to discuss.

Andrew Speakman 31 October 2013

ASTRA Clinical Data Reference Tables

Note CHIC Codes should be supplied for fields in bold – see the CHIC Codes table below

Table 1 – Demographic information table

This is a subset of the UK CHIC PATIENTCENTRE table with sensitive patient identifiable information removed

Field Name	*Description*	*Type*
StudyID	ASTRA study unique patient identifier	text (5)
DOB	Date of birth	dd/mm/yyyy
HIVPos	Date of first known positive HIV antibody test	dd/mm/yyyy
HIVNeg	Date of last negative HIV antibody test	dd/mm/yyyy
Firstseen	Date of first HIV attendance at centre	dd/mm/yyyy
Lastseen	Date when last seen *by a clinician* at the centre	dd/mm/yyyy
ExposureID	HIV exposure category	integer
DiedID	Is patient known to have died code	integer
DDeath	Date of death	dd/mm/yyyy
Cause	Cause of death (where known)	text (60+)

Table 2 – AIDS events table

This is the same format as the UK CHIC AIDSEVENT table- please include all AIDS events for each individual

Field Name	*Description*	*Type*
StudyID	ASTRA study unique patient identifier	text (5)
DOB	Date of birth	dd/mm/yyyy
DAIDS	Date of AIDS event	dd/mm/yyyy
AIDSID	AIDS event code	integer

Table 3 – Antiretroviral treatment table

This is the same format as the UK CHIC ANTIRETRO table- please include all ARVs ever taken for each individual

Field Name	*Description*	*Type*
StudyID	ASTRA study unique patient identifier	text (5)
DOB	Date of birth	dd/mm/yyyy
DStart	Date started taking drug	dd/mm/yyyy
DStop	Date stopped taking drug	dd/mm/yyyy
DrugID	Drug code	integer (15)
ReasonStopID1	Reason for stopping drug	integer
ReasonStopID2	Reason for stopping drug (if multiple codes)	integer
ReasonstopID3	Reason for stopping drug (if multiple codes)	integer

Table 4 – CD4 count table

This is the same format as the UK CHIC CD4 table- please include all ARVs ever taken for each individual

Field Name	*Description*	*Type*
StudyID	ASTRA study unique patient identifier	text (5)
DOB	Date of birth	dd/mm/yyyy
Dlab	Date of lab measurement	dd/mm/yyyy
CD4A	Absolute CD4 count in cells/mm^3	integer
CD4P	CD4 percentage	number (1dp)
CD8A	Absolute CD8 count in cells/mm^3	integer
CD8P	CD8 percentage	number (1dp)

Table 5 – Viral load table

This is the same format as the UK CHIC RNA/HIV Viral Load table- please include all VLs available for each individual

Field Name	*Description*	*Type*
StudyID	ASTRA study unique patient identifier	text (5)
DOB	Date of birth	dd/mm/yyyy
Dlab	Date of lab measurement	dd/mm/yyyy
RNA	HIV Viral Load level in copies/ml	long integer
UndetID	Status of HIV RNA measurement code	integer
AssayID	HIV RNA assay code	integer

Table 6 – Hepatitis table

This is the same format as the UK CHIC HEPATITIS table- please include all test results available for each individual

Field Name	*Description*	*Type*
StudyID	ASTRA study unique patient identifier	text (5)
DOB	Date of birth	dd/mm/yyyy
DHeptest	Date of hepatitis test	dd/mm/yyyy
HepTestID	Hep test code	integer
HepResultID	test result (-/+/indet)	integer
Hepvalue	test result value, e.g. RNA copies	long integer
UndetID	Result status: below/within/above assay limit	integer
HepUnitID	test result units	integer

Table 7 – Toxicity table

This is the same format as the UK CHIC TOXICITY table- please include all test results available for each individual

Field Name	*Description*	*Type*
StudyID	ASTRA study unique patient identifier	text (5)
DOB	Date of birth	dd/mm/yyyy
DToxtest	Date of toxicity test	dd/mm/yyyy
ToxTestID	Tox test code	integer
ToxResult	Test result value	integer
ToxUnitID	Test results units	text (10)

Table 8 – Serious non AIDS events table

This is the same format as the UK CHIC Serious Non AIDS Events table - please include all known events for each individual

Field Name	*Description*	*Type*
StudyID	ASTRA study unique patient identifier	text (5)
DOB	Date of birth	dd/mm/yyyy
DSerNA	Date of serious Non-AIDS event	dd/mm/yyyy
SNAID	Serious Non-AIDS event code	integer
SNAConf	Serious Non-AIDS event status, whether Confirmed/Probable/Status unknown	integer
ICDcode	ICD code if used	text
SNOMEDcode	SNOMED code if used	text

Table 9 – Hospital admissions table

This is a new table specific to ASTRA- if available, please include all hospital admissions for each individual

Field Name	*Description*	*Type*
StudyID	ASTRA study unique patient identifier	text (5)
DOB	Date of birth	dd/mm/yyyy
DAdmission	Date of hospital admission	dd/mm/yyyy
AdmitReason	Reason for hospital admission (hospital code with translation table supplied separately)	Integer or text (60+)
DDischarge	Date of hospital discharge, if known	dd/mm/yyyy

UK CHIC CODES (November 2013)

Field	Information
Code	Lookup
AIDSID	**AIDS**
1	Bacterial infections (multiple or recurrent) at age < 13 years
2	Candidiasis, oesophageal
3	Candidiasis, trachea/bronchi/lungs
4	Candidiasis, site unknown
5	Cervical cancer, invasive
6	Coccidioidomycosis, extrapulmonary
7	Cryptococcosis, extrapulmonary
8	Cryptosporidiosis, duration > 1 month
9	Cytomegalovirus retinitis
10	Cytomegalovirus disease, other
11	Cytomegalovirus, site unknown
12	Herpes simplex disease, duration > 1 month
13	Histoplasmosis, extrapulmonary and/or disseminated
14	HIV Encephalopathy
15	Isosporiasis, duration > 1 month
16	Kaposi's sarcoma
17	Lymphoid interstitial pneumonia or pulmonary lymphoid hyperplasia at age <13 years
18	Lymphoma, Burkitt's, immunoblastic or equivalent
19	Lymphoma, primary in brain
20	Mycobacterium avium, extrapulmonary (MAI/MAC)
21	Mycobacterium tuberculosis, pulmonary
22	Mycobacterium tuberculosis, extrapulmonary
23	Mycobacterium, other (disseminated)
24	Pneumoncystis carinii pneumonia (P. jiroveci)
25	Pneumonia, recurrent in a 12-month period
26	Progressive multifocal leukoencephalopathy
27	Salmonella Septicaemia, recurrent
28	Toxoplasmosis, cerebral
29	HIV wasting syndrome
31	Lymphoma Site Unknown
51	Mycobacterium tuberculosis, Site Unknown
98	AIDS disease, not specified
99	Not Known
AssayID	**Assay**
1	Roche v1.0 (<400)
2	Roche non-B (<400)
3	Roche v1.5 (<400)
4	Roche v1.5 US (<50)
5	Roche – version unknown
6	Cobas v1.5 (<400)
7	Cobas v1.5 US (<50)
9	Cobas – version unknown
10	NASBA (<400)
11	NASBA US
12	NASBA – version unknown
13	Chiron b-DNA v1.0
14	Chiron b-DNA v2.0 (<500)
15	Chiron b-DNA v3.0 US (<50) (also known as Bayer?)

16	Chiron – version unknown
17	Nuclisens (<400)
18	Nuclisens US (<50?)
19	Nuclisens – version unknown
21	Cobas<10 copy assay
22	Abbott RealTime HIV-1 (ultra-sensitive)
23	Abbott LCx HIV RNA
29	Roche Cobas TaqMan v1.0 (<40)
30	Roche Cobas TaqMan v2.0 (<20)
31	Abbott RealTime HIV-1 (<40)
98	Other
99	Not known
DiedID	**Died**
0	No
1	Yes
99	Not known
DrugID	**Drug**
1	Zidovudine (AZT)
2	Zalcitabine (ddC)
3	Didanosine (ddI)
4	Stavudine (d4T)
5	Lamivudine (3TC)
6	Abacavir
7	Combivir (AZT+3TC)
8	Lodenosine
9	Trizivir (AZT + 3TC + abacavir)
10	Tenofovir (TDF)
11	Emtricitabine (FTC)
12	Kivexa (3TC + Abacavir)
13	Truvada (Tenofovir/TDF + emtricitabine /FTC)
14	Tenofovir alafenamide fumarate (TAF)
19	Other NRTI
20	Nevirapine
21	Efavirenz
22	Loviride
23	Delavirdine
24	Etravirine / TMC125
25	Rilpivirine (RPV)
26	Eviplera (rilpivirine + tenofovir/TDF + emtricitabine/FTC)
39	Other NNRTI
40	Saquinavir hard gel (invirase)
41	Indinavir
42	Ritonavir – any dose
43	Nelfinavir
44	Saquinavir soft gel (fortovase)
45	Amprenavir
46	Lopinavir (ABT 378) (kaletra)
47	Saquinavir (form unknown)
48	Atazanavir
49	Other PI
50	Hydroxyurea / hydroxycarbamide
51	IL-2

60	Acyclovir
61	Fos amprenavir
62	Tipranavir
63	Darunavir / TMC114
70	Enfuvirtide / T20
80	Adefovir
90	Blinded treatment in clinical trial
95	Maraviroc
96	Vicriviroc
97	Other Entry (CCR5) Inhibitor
98	Other ART drug (ART drug is known, but not on this list)
99	Not known (ART, but not known which drug)
110	Raltegravir / MK-0518
111	elvitegravir
112	dolutegravir
119	Other Integrase Inhibitor
120	Atripla (Efavirenz/Tenofovir/Emtricitabine)
121	STRIBILD™ (QUAD) ((elvitegravir + cobicistat + emtricitabine + tenofovir disoproxil fumarate)
122	(dolutegravir/lamivudine/abacavir)
130	cobicistat
131	cobicistat/atazanavir
132	cobicistat/darunavir
133	cobicistat/elvitegravir
ExposureID	**Exposure**
1	Homosexual/bisexual (including homo / bi sex who **also** injected drugs)
2	Injecting drug use
3	Heterosexual
4	Blood/blood products recipient
5	Mother-to-child transmission
98	Other
99	Not Known
HepResultID	**HepResult**
0	Negative
1	Positive
2	Indeterminate /weakly reactive/equivocal
HepTestID	**HepTest**
1	Hep A antibody (total)
2	Hep B surface antigen (HbsAg)
3	Hep B surface antibody (anti-HBs)
4	Hep B core antibody (anti-HBc)
5	Hep B e antigen
6	Hep B e antibody
7	Hep C antibody
8	Hep C virus PCR/bDNA
9	Hep B core antibody (IgM)
10	Hep A antibody (IgM)
11	Hep B DNA (Type unknown)
12	Hep D antibody (total)
13	Hep B surface antigen (titre)
14	Hep D antibody (IgM)
98	Other

99	Not known
HepUnitID	**HepUnit**
1	IU/mL
2	copies/mL
98	Other
99	Not known
ReasonStopID	**ReasonStop**
10	Failure-cause unknown
11	Virological
12	Immunological
13	Clinical
14	VL / CD4
20	Toxicity-type unknown
30	Skin
31	Hypersensisity – Abacavir
32	Rash
40	GI
41	Nausea/Vomiting
42	Diarrhoea
43	Pancreatitis
44	Abnormal LFT
50	Neuro
51	CNS Disturbance
52	Peripheral Neuropathy
53	Headache
60	Metabolic
61	Lipids
62	Glucose Intolerance
63	Hyperlactataemia
64	Osteopaenia
70	Lipodystrophy
80	Myelotoxicity
81	Anaemia
82	Neutropenia
83	Thrombocytopenia
91	Myotoxicity
92	Nephrolithiasis/Renal Dysfunction
100	Patient Choice
110	Clinician decision
120	Interaction
130	Simplification
140	Poor Adherence
150	Joined clinical trial
160	Study/Trial End
170	New drug available
180	Known treatment interruption
190	Protocol amendment
200	Pregnancy
201	At start/during pregnancy
202	End of short-course ART
210	Intercurrent illness, not HIV/ drug related
220	VL sufficiently low

230	CD4 sufficiently high
240	Regimen change
250	Transfer of care
260	Drug Experience / Resistance
998	Other
999	Not Known
SNAConf	**Serious Non-AIDS event Confirmed**
1	Confirmed
2	Probable
99	Status Unknown (not known whether Confirmed or Probable)
SNAID	**Serious Non-AIDS**
10	Acute Myocardial Infarction (AMI)
11	Congestive Heart Failure (CHF)
12	Coronary Artery Disease Requiring Drug Treatment
13	Coronary Revascularization (coronary angioplasty, artery by-pass grafting, stent, carotic endarterectomy
50	Decompensated Liver Disease (DLD)
51	Alcoholic liver disease
52	Liver Cirrhosis
53	Liver Fibrosis
56	HAART associated liver disease (including non-alcoholic steatohepatosis, nodular regenerative hyperplasia, hepatoportal sclerosis
58	Liver disease, other
59	Liver disease, chronic, unspecified
70	Diabetes Mellitus (DM)
75	Lactic acidosis, symptomatic
80	End Stage Renal Disease (ESRD)
81	HIV nephropathy
82	HAART associated renal failure (including Fanconi syndrome)
89	Renal disease, other
100	Anal cancer
101	Bowel cancer
102	Breast cancer
103	Castleman's disease
104	Cervical cancer
105	Hodgkins Lymphoma (HL)
106	Liver cancer
107	Lung cancer
108	Stomach cancer
109	Prostate cancer
110	Other Non-AIDS-Defining cancer (NADC), unspecified
120	Peripheral Arterial Disease (PAD)
121	Pulmonary Embolism (PE)
122	Deep Vein Thrombosis (DVT)
123	Stroke
129	Other vascular / thromboembolic disease
130	Osteopenia
131	Osteoporosis
132	Fracture, fragility
133	Fracture, traumatic
134	Fracture, mixed (traumatic+fragility)
135	Fracture, unspecified
138	Other bone disease

139	Bone disease, unspecified
140	Sepsis (or Sepsis Syndrome)
141	Multi-organ failure
142	Haemophagocytic Syndrome
143	Bacterial infection, severe (non-sepsis)
144	Fungal infection, severe
145	Viral infection, severe
149	Infection, severe, unspecified (non-AIDS)
998	Serious Non-AIDS event, other
999	Serious Non-AIDS event, not specified
ToxTestID	**ToxTest**
1	ALT
2	Albumin
3	Alkaline phosphatase
4	Amylase
5	AST
6	Bilirubin
7	Cholesterol total (non fasting or unknown)
8	CPK (creatine phosphokinase)
9	Creatinine (serum)
10	Glucose
11	GGT(g-glutamyl transferase)
12	Haemoglobin
13	HDL
14	Lactate
15	LDL
16	Triglycerides
17	Urea
18	Lactate dehydrogenase
19	Cholesterol (fasting)
20	Protein Total (urine)
21	Creatinine (urine)
22	Protein/Creatinine Ratio (PCR) (urine)
23	Albumin (urine)
24	Albumin/Creatinine Ratio (ACR)
25	Protein 24hr (urine)
26	Platelet count
27	Vitamin D
28	Phosphate (serum)
29	Calcium (serum)
30	Parathyroid hormone (PTH)
31	Calcium (serum, corrected)
98	Other
99	Not known
ToxUnitID	**ToxUnit**
1	IU/L
2	g/L
3	U/L
4	µmol/L
5	µmol/L (plasma)
6	mmol/L
7	mmol/L (urine)

8	g/dL
9	mg/L
10	mg/mmol
11	g/day
12	mg/day
13	µg/L (micrograms per litre)
14	ng/L (nanograms per litre)
15	10^9/L
16	mg/dL
17	pg/ml
18	nmol/L
19	pmol/L
98	Other
99	Not known
UndetID	**Undet**
-1	< Below lower limit of detectability
0	Any value that is detectable but below the upper limit of quantification
1	> Above upper limit of quantification

Appendix VIII. Risk, rate and odds

Risk, rate and odds are all used to describe how often an event occurs. In a population with N individuals, n is the number of people who have the outcome over a follow-up time of length t, thus $N - n$ is the number of people who do not have the outcome. The probability of an outcome is p, hence $1 - p$ is the probability of not having the outcome. Using this notation, risk is defined as:

$$(Incidence)Risk = \frac{Number\ of\ people\ with\ the\ event\ during\ follow-up}{The\ total\ number\ of\ people\ in\ the\ population} = \frac{n}{N} = p$$

rates are defined as:

$$(Incidence)Rate = \frac{Number\ of\ people\ with\ the\ event\ during\ follow-up}{Total\ number\ of\ person-years\ at\ risk\ during\ follow-up} = \frac{n}{t}$$

And odds are defined as:

$$Odds = \frac{Number\ of\ people\ with\ the\ outcome\ during\ follow-up}{Number\ of\ people\ without\ the\ outcome\ during\ follow-up} = \frac{n}{N-n}$$
$$= \frac{Np}{N(1-p)} = \frac{p}{1-p}.$$

It is possible to convert from odds to risk:

$$Odds = \frac{p}{1-p} = \frac{Risk}{1-Risk}.$$

Effect measures are defined using these concepts. These enable comparisons between groups in order to understand associations. Common measures are the risk ratio/relative risk (RR), odds ratio (OR) and rate ratio, which are defined below. These definitions use the following notation: n_1 is the number of individuals with a certain outcome of interest, if a member of group one and likewise n_2 if a member of group two; p_1 is the probability of an outcome if a member of group one and p_2 if a member of group two; t_1 is the total follow-up time for group one and t_2 for group two.

The risk ratio (RR) is defined as:

$$RR = \frac{Risk_1}{Risk_2} = \frac{p_1}{p_2}$$

the rate ratio as:

$$Rate\ ratio = \frac{Rate_1}{Rate_2} = \frac{\frac{n_1}{t_1}}{\frac{n_2}{t_2}}$$

And the odds ratio (OR) is defined as:

$$OR = \frac{Odds_1}{Odds_2} = \frac{\frac{p_1}{(1 - p_1)}}{\frac{p_2}{(1 - p_2)}}.$$

Appendix IX. Generalised linear model (GLM)

GLM are models where the dependent variable is assumed to follow an exponential family distribution with its mean μ equal to some linear function of the independent variables $x_1 - x_n$:

$$g(\mu) = \beta_0 + \beta_1 x_1 + \beta_2 x_2 + \cdots + \beta_n x_n.$$

There are three components to a GLM, the random component (or error model), systematic component and link function. The random component is the probability distribution of the dependent variable. The systematic component specifies the linear combination of the independent variables. The link function states the link between the random and systematic components. Examples of GLMs include linear, logistic, log-linear, and Poisson regression:

Model (GLM)	**Random component distribution of y**	**Link function**
Linear	Normal	Identity μ
Logistic	Binomial	Logit $\log\frac{\mu}{1-\mu}$
Log-linear	Poisson	Log $\ln\mu$
Poisson	Poisson	Log $\ln\mu$

There are four assumptions that must hold for GLMs:

1. Independence of each data points,
2. Correct distribution of the residuals,
3. Correct specification of the variance structure,
4. Linear relationship between the response and the linear predictor.

The definition of the GLM is a way of unifying the various statistical models, a number of which are used throughout this thesis and are therefore defined in the proceeding appendices.

Appendix X. Linear regression

Linear regression is the simplest example of a GLM. A simple linear regression model contains only one covariate, whereas a multiple linear regression model contains two or more covariates:

$$y = \beta_0 + \beta_1 x + \varepsilon$$

$$y = \beta_0 + \beta_1 x_1 + \beta_2 x_2 + \cdots + \beta_n x_n + \varepsilon.$$

In these equations, y is the dependent variable, x_1 to x_n are the independent variables, β_0 to β_n are the coefficients determined in the analysis, and ϵ is the residual error term. The intercept term is denoted by β_0 and is expected value of the dependent variable y when all of the $x_i = 0$.

There are five main assumptions for the multiple linear regression model. Firstly, the association between dependent and independent variables is assumed to be linear and additive. This can be tested by scatter plots of the response against each covariate where the points should roughly have a straight-line relationship. Secondly, all residuals are assumed to be normally distributed. This can be tested with histogram plots. Thirdly there is assumed to be little multicollinearity between the independent variables and they must be uncorrelated with the error terms (i.e. the mean of the dependent variable must be uncorrelated with the independent variables). This can be checked with a correlation matrix. Additionally, there is assumed to be little or no autocorrelation in the data, i.e. the error terms must be independently distributed across the observations. Finally, there is assumed to be constant variance of the residual error terms across all values of the dependent variable (homoscedasticity). Again, the last two assumptions can be checked with scatter plots of the residual error.

In order to estimate the regression line which best fits the data, two methods are generally used – least squares or maximum likelihood estimation (MLE). The least squares method estimates the unknown coefficients $\beta_0 - \beta_n$ by minimising the sum of the squared differences between the model and the data. The maximum likelihood method estimates the unknown parameters by maximising the known likelihood distribution (the likelihood of a set of parameter values given the observed data). In other words, MLE aims to find the parameter values that make the observed data most likely.

Appendix XI. Logistic regression

For logistic regression the independent variables may be continuous, categorical or binary. Instead of classifying an observation into either the $y = 0$ or $y = 1$ group, logistic regression predicts the probability p that an indicator variable is equal to 1. Since probabilities are restricted to the range (0,1) the logit link function or log odds function, $\log\frac{\mu}{1-\mu}$, is used in order to transform this so that the independent variables can take any value from minus to plus infinity. The logistic regression model is defined as:

$$\log\frac{p}{1-p} = \beta_0 + \beta_1 x_1 + \beta_2 x_2 + \cdots + \beta_n x_n$$

where $\boldsymbol{p}$ is the probability that the dependent variable $\boldsymbol{y = 1}$. The odds is given by exponentiation[834]:

$$e^{\log\left(\frac{p}{1-p}\right)} = e^{(\beta_0 + \beta_1 x_1 + \beta_2 x_2 + \cdots + \beta_n x_n)}$$

$$\frac{p}{1-p} = odds = e^{\beta_0} \times e^{\beta_1 x_1} \times e^{\beta_2 x_2} \times \ldots \times e^{\beta_n x_n}$$

In a logistic regression model with two independent variables x_1 and x_2, if the value of x_2 was fixed (adjusted for), then the coefficient e^{β_1} can be interpreted as an estimate of the additional effect of having the covariate of interest x_1 on a multiplicative scale. Hence logistic regression produces ORs in order to assess associations. ORs from a model which contains more than one independent variable are generally known as adjusted odds ratios (aORs):

For $x_1 = 0$:

$$odds = e^{\beta_0} \times e^0 \times e^{\beta_2 x_2} = e^{\beta_0} \times e^{\beta_2 x_2},$$

and for $x_1 = 1$:

$$odds = e^{\beta_0} \times e^{\beta_1} \times e^{\beta_2 x_2}.$$

Thus the odds ratio is

$$OR = \frac{odds\ when\ x_1 = 1}{odds\ when\ x_1 = 0} = \frac{e^{\beta_0} \times e^{\beta_1} \times e^{\beta_2 x_2}}{e^{\beta_0} \times e^{\beta_2 x_2}} = e^{\beta_1}.$$

Appendix XII. Poisson regression

Poisson regression is generally used for data where the response variable is a count. It is best for rare events, which tend to follow a Poisson distribution, whereas common events tend to follow a normal distribution. The Poisson regression model is defined as:

$$\log \mu = \beta_0 + \beta_1 x_1 + \beta_2 x_2 + \cdots + \beta_n x_n$$

$$\mu = e^{\beta_0 + \beta_1 x_1 + \beta_2 x_2 + \cdots + \beta_n x_n}.$$

Poisson regression can also be used to model a rate, $\frac{y}{t}$, where t is an interval of time. The length of time can vary from observation to observation so the model needs to consider time; this is described below, where $\log t$ is known as the offset term.

$$\log \frac{\mu}{t} = \beta_0 + \beta_1 x_1 + \beta_2 x_2 + \cdots + \beta_n x_n + \varepsilon$$

$$\log \mu - \log t = \beta_0 + \beta_1 x_1 + \beta_2 x_2 + \cdots + \beta_n x_n + \varepsilon$$

$$\log \mu = \beta_0 + \beta_1 x_1 + \beta_2 x_2 + \cdots + \beta_n x_n + \varepsilon + \log t$$

Appendix XIII. Modified Poisson regression

Poisson regression may be used to estimate binomial distributed data rather than logistic regression. However, when using this method the error for the estimated relative risk will be overestimated[835]. This problem can be remedied by using sandwich estimation to robustly estimate error variance, which is commonly referred to as modified Poisson regression. This method is outlined below.

In a situation where x_i is a binary exposure, with $x_i = 0$ if unexposed and $x_i = 1$ if exposed, then data can be summarised as displayed in the following table:

	Y=1 (event)	Y=0 (no event)	Total
X=1 (exposed)	A	B	$n_1 = a + b$
X=0 (unexposed)	C	D	$n_2 = c + d$
			$N = n_1 + n_2$

The exponent of the intercept is the risk of an event in the unexposed group:

$$\exp(\widehat{\beta_0}) = \frac{c}{n_0}.$$

In the case of the binary outcome the exponent of the coefficient $\beta_i$is a risk ratio (RR):

$$\exp(\hat{\beta}_j) = \frac{an_0}{cn_1} = \widehat{RR}$$

With the estimated variance for the RR of:

$$Var(\widehat{RR}) = \frac{1}{a} + \frac{1}{c}.$$

Sandwich estimation is then used to obtain a more robust error variance[526]. The Corrected variance is:

$$Var(\widehat{RR}) = \frac{1}{a^2}\sum_{i=1}^{n_1}(y_i - \exp[\beta_0 + \beta_1 + \cdots + \beta_n])^2 + \frac{1}{c^2}\sum_{i=1}^{n_0}(y_i - \exp[\beta_0 + \beta_1 + \cdots + \beta_n])^2$$

and is consistently estimated as:

$$Var(\widehat{RR}) = \frac{1}{a} - \frac{1}{n_1} + \frac{1}{c} - \frac{1}{n_0}.$$

Appendix XIV. Cox proportional hazards model

In order to define the Cox proportion hazards model, one must first consider the survivor and hazard functions. The survivor function denotes the probability of survival at time t as shown below, with the opposite being $\mathrm{F(t)}$, the cumulative probability of failure at time t:

$$S(t) = 1 - F(t).$$

In the definition of the hazard function below, t are the survival times, $\mathrm{f(t)}$ is the density function (or probability distribution for the dependent variable) and $\mathrm{S(t)}$ is the survivor function defined above:

$$h(t) = \frac{f(t)}{S(t)}.$$

The Cox proportional hazards model is defined below and is of the same form as all other GLM, where the coefficients are the estimated regression coefficients and the $\boldsymbol{x_n}$ are the independent variables.

$$Log\big(h(t)\big) = \log\big(h_0(t)\big) + \beta_1 x_1 + \beta_2 x_2 + \beta_3 x_3 + \cdots + \beta_n x_n$$

$$h(t) = e^{\log\left(h_0(t)\right) + \beta_1 x_1 + \beta_2 x_2 + \beta_3 x_3 + \cdots + \beta_n x_n}$$

The intercept term here is analogous to the baseline hazard $\log\big(h_0(t)\big)$, that is the hazard of an event occurring when all levels of the independent variables are set to 0.

Cox proportional hazards models are semi-parametric since there is no functional form assumed for the baseline hazard function. Two key assumptions need to be met for the Cox proportional hazards model to be applicable. Firstly, non-informative censoring – the censoring of individuals should not be associated with the probability of an event occurring. Secondly, the proportional hazards assumption – survival curves for two strata must have constant relative hazard functions over time.

Below is an outline of how the hazard ratios relate directly to the variable coefficients in an example with two independent variables x_1 and x_2, where the value of x_2 is held fixed.

Group a are individuals for whom $x_1 = a$, and group b are individuals for whom $x_1 = b$

$$Hazards\ for\ group\ a = \ h_a(t) = \ e^{\log\left(h_0(t)\right)} \times e^{\beta_1 a} \times e^{\beta_2 x_2} = \ h_0(t) \times e^{\beta_1 a} \times e^{\beta_2 x_2},$$

$$Hazards\ for\ group\ b = \ h_b(t) = \ e^{\log(h_0(t))} \times e^{\beta_1 b} \times e^{\beta_2 x_2} = \ h_0(t) \times e^{\beta_1 b} \times e^{\beta_2 x_2}.$$

Thus the hazard ratio is

$$HR = \frac{hazards\ for\ group\ a}{hazards\ for\ group\ b} = \frac{h_0(t) \times e^{\beta_1 a} \times e^{\beta_2 x_2}}{h_0(t) \times e^{\beta_1 b} \times e^{\beta_2 x_2}} = \frac{e^{\beta_1 a}}{e^{\beta_1 b}} = \ e^{\beta_1 (a-b)}.$$

Appendix XV. Generalised estimating equations

A model using GEEs extends the GLMs described in Appendix IX. so that the distribution does not need to be fully specified; therefore, the outcome is modelled using the same link function and systematic component as if the observations were independent. The random component must additionally specify the correlation (or covariance) structure for the responses as the error terms are no longer independent as assumed previously. GEEs use quasi-likelihood estimation rather than maximum likelihood estimation or ordinary least squares.

One of four correlation structures is generally assumed:

- Independence $\begin{bmatrix} 1 & 0 & 0 \\ 0 & 1 & 0 \\ 0 & 0 & 1 \end{bmatrix}$
- Exchangeable $\begin{bmatrix} 1 & \rho & \rho \\ \rho & 1 & \rho \\ \rho & \rho & 1 \end{bmatrix}$
- Autoregressive $\begin{bmatrix} 1 & \rho & \rho^2 \\ \rho & 1 & \rho \\ \rho^2 & \rho & 1 \end{bmatrix}$
- Unstructured $\begin{bmatrix} 1 & \rho_{12} & \rho_{13} \\ \rho_{12} & 1 & \rho_{23} \\ \rho_{13} & \rho_{23} & 1 \end{bmatrix}$

Where ρ is the correlation parameter and $\rho_{ij} = correlation(y_{ij}, y_{ik})$ for the i^{th} individual/hospital at times j and k. The independent correlation structure assumes that responses within each cluster are independent. The exchangeable correlation structure indicates that the responses within each cluster are equally correlated. The autoregressive structure denotes that the further apart (e.g. in time) the responses are, the weaker their correlation with each other. This is generally a reasonable assumption for data where the response is repeated measures for each participant studied. The unstructured correlation structure is flexible and does not make any assumptions about the correlations within clusters. However, this usually requires estimation of a large number of additional parameters ($\rho_{12}, \rho_{12}, \rho_{12}, \ldots$) in comparison to the standard GLM and when an exchangeable or autoregressive correlation structure is assumed. This could cause poor estimation of the parameters when there are large clusters or clusters of varying sizes.

Advantages of GEEs include that no assumptions about the distribution of the correlated response variable are required, and only the mean and variance must be specified. Additionally, even if the choice of the correlation matrix is false, the solution

to the GEE is consistent (tends towards the true value as the size of the dataset increases) and approximately normally distributed. However, correctly specifying of the correlation matrix can increase the accuracy of the estimates and decrease their standard errors.

Appendix XVI. Publications and presentations arising from this work

[Chapter 2] Burch LS, Smith CJ, Phillips AN, Johnson MA, Lampe FC. Socioeconomic status and response to antiretroviral therapy in high-income countries: a literature review. Aids. 2016 May 15;30(8):1147-62.

[Chapter 6] Burch LS, Smith CJ, Phillips AN, Johnson MA, Lampe FC. Is the gender difference in virological response to ART declining over time? 5th International Workshop on HIV & Women, February 21-22 2015, Seattle, Washington. Oral abstract 14.

[Chapter 6] Burch L, Smith C, Lampe F, et al. Is the gender difference in viral load response to ART narrowing over time? 15th European AIDS Conference; Oct 21-24 2015; Barcelona, Spain; Oral abstract PS6/3.

[Chapter 7] Burch L, Smith C, Anderson J, et al. Socio-economic factors and virological suppression among people diagnosed with HIV in the United Kingdom: results from the ASTRA study. HIV Drug Therapy Glasgow meeting November 2-6 2014 Glasgow, UK; Poster P001.

[Chapter 7] Burch L, Smith C, Anderson J, et al. Socioeconomic Factors and Virological Rebound: A Prospective UK Cohort Study]. CROI 2015 Conference on Retroviruses and Opportunistic Infections; Feb 23-26 2017; Seattle, Washington; Abstract 560.

[Chapter 7] Burch LS, Smith CJ, Anderson J, et al. Socioeconomic status and treatment outcomes for individuals with HIV on antiretroviral treatment in the UK: cross-sectional and longitudinal analyses. The Lancet. Public Health. 2016 Nov 1;1(1):e26.

[Chapter 8] O'Connell R, Burch L, Anderson J, et al. Do Socio-economic Factors Explain Gender Differences in Virological Response to ART in the UK? 15th European AIDS Conference; Oct 21-24 2015; Barcelona, Spain; Oral abstract PS6/5.

[Chapter 9] Burch L, Oakes-Monger N, Smith C, et al. Socio-economic factors and late diagnosis of HIV in 2011-2013 in the Royal Free cohort. 3rd joint Conference of the British HIV Association (BHIVA) with the British Association for Sexual Health and HIV (BASHH), Liverpool, UK Apr 1-4 2014; Poster 285.

Socioeconomic status and treatment outcomes for individuals with HIV on antiretroviral treatment in the UK: cross-sectional and longitudinal analyses

Lisa S Burch, Colette J Smith, Jane Anderson, Lorraine Sherr, Alison J Rodger, Rebecca O'Connell, Anna-Maria Geretti, Richard Gilson, Martin Fisher*, Jonathan Elford, Martin Jones, Simon Collins, Yusef Azad, Andrew N Phillips, Andrew Speakman, Margaret A Johnson, Fiona C Lampe, for the Antiretrovirals, Sexual Transmission Risk and Attitudes (ASTRA) Study Group

Summary

Background Few studies have assessed the effect of socioeconomic status on HIV treatment outcomes in settings with universal access to health care. Here we aimed to investigate the association of socioeconomic factors with antiretroviral therapy (ART) non-adherence, virological non-suppression, and virological rebound, in HIV-positive people on ART in the UK.

Methods We used data from the Antiretrovirals, Sexual Transmission Risk and Attitudes (ASTRA) questionnaire study, which recruited participants aged 18 years or older with HIV from eight HIV outpatient clinics in the UK between Feb 1, 2011, and Dec 31, 2012. Participants self-completed a confidential questionnaire on sociodemographic, health, and lifestyle issues. In participants on ART, we assessed associations of financial hardship, employment, housing, and education with: self-reported ART non-adherence at the time of the questionnaire; virological non-suppression (viral load >50 copies per mL) at the time of questionnaire in those who started ART at least 6 months ago (cross-sectional analysis); and subsequent virological rebound (viral load >200 copies per mL) in those with initial viral load of 50 copies per mL or lower (longitudinal analysis).

Findings Of the 3258 people who completed the questionnaire, 2771 (85%) reported being on ART at the time of the questionnaire, and 2704 with complete data were included. 873 (32%) of 2704 participants reported non-adherence to ART and 219 (9%) of 2405 had virological non-suppression in cross-sectional analysis. Each of the four measures of lower socioeconomic status was strongly associated with non-adherence to ART, and with virological non-suppression (prevalence ratios [PR] adjusted for gender/sexual orientation, age, and ethnic origin: greatest financial hardship *vs* none 2·4, 95% CI 1·6–3·4; non-employment 2·0, 1·5–2·6; unstable housing *vs* homeowner 3·0, 1·9–4·6; non-university education 1·6, 1·2–2·2). 139 (8%) of 1740 individuals had subsequent virological rebound (rate=3·6/100 person-years). Low socioeconomic status was predictive of longitudinal rebound risk (adjusted hazard ratio [HR] for greatest financial hardship *vs* none 2·3, 95% CI 1·4–3·9; non-employment 3·0, 2·1–4·2; unstable housing *vs* homeowner 3·3, 1·8–6·1; non-university education 1·6, 1·1–2·3).

Interpretation Socioeconomic disadvantage was strongly associated with poorer HIV treatment outcomes in this setting with universal health care. Adherence interventions and increased social support for those most at risk should be considered.

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See Comment page e6

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Introduction

Substantial evidence exists of socioeconomic inequalities in the prognosis of chronic diseases. In Europe and the USA, socioeconomic factors such as poverty, low income, and low education level have been associated with poorer outcomes for several diseases, including cancer, and cardiovascular disease.[1–3] Findings of other studies have suggested that lower socioeconomic status (measured by education or income) is associated with poorer adherence to treatment, such as steroids for asthma[4] and insulin for diabetes.[5]

HIV is a disease that disproportionately affects those with socioeconomic disadvantage.[6] In the USA, in people with HIV receiving antiretroviral therapy (ART), lower levels of socioeconomic status (as indicated by lower education level, unemployment, homelessness, or household poverty) are associated with having poorer virological and immunological outcomes.[7–11] HIV-positive populations in the UK and Europe also comprise distinct demographic groups, with substantial variation in social circumstances. As such, social inequalities may result in disparities in HIV health outcomes. However, in contrast to the USA, the UK has universal free access to health care, including HIV diagnosis, hospital consultations, and antiretroviral treatment, which should greatly lessen financial barriers

Research in context

Evidence before this study

We searched PubMed for studies assessing the associations between socioeconomic status and HIV treatment outcomes (search originally done in June, 2015, updated in February, 2016, and published in May, 2016). The papers included in the review were original research studies of any design and including secondary observational analyses of randomised controlled trial data in which the criteria for inclusion were: written in English; set in high-income countries; included more than 100 participants; recruitment not entirely before the modern highly active antiretroviral therapy era (ie, some recruitment after 2001); all participants prescribed antiretroviral therapy (ART); not solely reporting analyses adjusted for adherence. We used the following MeSH terms: "HIV" and any of "socioeconomic" or "socio-economic" or "antiretroviral" or "ART" with any "virologic" or "virological" or "immunologic" or "immunological" or "failure" of "rebound" or "suppression" or "viral load" or "CD4" or "education level" or "employment" or "housing" or "occupation" or "deprivation" or "poverty" or "income" or "insurance". 46 studies met the entry criteria, of which, ten (71%) of 14 noted an association between lower socioeconomic status and poorer virological response, four (67%) of six found an association between lower socioeconomic status and poorer immunological response, and 23 (66%) of 35 found an association between lower socioeconomic status and ART non-adherence. Most studies have been done in the USA (ie, without universal free access to health care) and have focused mainly on education rather than markers of current poverty and hardship. No previous studies have been done of socioeconomic status and ART response in people with HIV in the UK.

Added value of this study

Our study provides evidence, from both cross-sectional and longitudinal analyses, that socioeconomic disadvantage (measured by financial hardship, non-employment, unstable housing status, and lower educational level) is an important determinant of HIV treatment outcomes in a setting with universal free access to health care and high rates of treatment success. Thus, our data suggest that the adverse effect of socioeconomic disadvantage goes beyond the ability to access or pay for treatment and care.

Implications of all the evidence

Collection of information about socioeconomic factors in a routine clinical care setting is key to identifying individuals at greater risk of poorer virological response to ART. Adherence and social support for socioeconomically disadvantaged individuals should be regarded as an important component of clinical care.

to accessing HIV treatment and care. Therefore, the associations between socioeconomic factors and HIV outcomes in the USA might not be generalisable to settings with free universal health care, which have been little studied.[6] Findings of two large European studies, the Swiss HIV Cohort study[11] and the Spanish CoRIS study,[12] showed that lower education level was associated with increased odds of viral load being higher than 50 copies per mL at 12 months after ART initiation (unadjusted odds ratios of 1·3 and 1·9, respectively); however, the Danish HIV Cohort study[13] noted no clear association. Additionally, in the Italian ICoNA cohort study[14] in individuals who had been taking ART for at least 6 months, unemployment was associated with double the risk of virological failure compared with working full-time. No previous studies have looked at socioeconomic variations in virological outcomes in people treated for HIV in the UK.

ART non-adherence is the major determinant of virological non-suppression and subsequent virological rebound,[15] which in turn predicts poorer prognosis for people living with HIV.[9,16] Thus, any effect of socioeconomic status on virological outcome is likely to be mediated to a great extent through differential patterns of adherence to HIV treatment. Findings of some European studies[9,10,17] have shown that lower socioeconomic status (measured by education, employment, and social support) is associated with ART non-adherence, but a minority of studies found no evidence.[10,11]

Here, with data from the Antiretrovirals, Sexual Transmission Risk and Attitudes (ASTRA) study, we aimed to investigate the association of socioeconomic factors with ART non-adherence, virological non-suppression, and virological rebound, in HIV-positive people on ART in the UK.

Methods

Study design and participants

ASTRA is a cross-sectional, questionnaire study of 3258 HIV-diagnosed individuals in the UK recruited from eight HIV outpatient clinics between Feb 1, 2011, and Dec 31, 2012.[18] Participants self-completed a confidential questionnaire on sociodemographic, health, and lifestyle issues. The most recent HIV viral load and CD4 count results available at the time of the questionnaire were recorded for all participants by study personnel. Six of the eight study clinics provided linkage to routine HIV clinical records (including serial viral load measurements) for consenting participants (2983 [92%]) using a pseudo-anonymised study number.

Demographic factors, socioeconomic factors, ART use and start date, and ART adherence were self-reported on the questionnaire. The demographic factors of interest were: gender/sexual orientation (men who have sex with men, heterosexual men, women), ethnic origin (white or non-white), and age (as a continuous variable). Men were classified as men who have sex with men if they self-identified as gay or bisexual, or reported sex with

For the ASTRA questionnaire see http://www.astra-study.org

a man in the past 3 months. Four markers of socioeconomic status were considered: ability to afford basic needs (financial hardship with four levels); employed (yes or no); housing status (homeowner; renting; unstable or other); and university education (yes or no). The following variables were additional markers of social circumstances: time living in the UK (UK born, >5 years, ≤5 years), English reading ability (UK born, fluent, not fluent), supportive network (most, medium, least), current stable partner (yes or no), and children (yes or no).

Financial hardship was derived from the question "Do you have enough money to cover your basic needs? (Eg, food and heating)" for which responses were: "Yes, all of the time"; "Yes, most of the time"; "Yes, some of the time"; "No". "Employed" included those who reported either full-time or part-time employment (or self-employment). For housing status, "rented" included those who rented privately or from the council or housing association; "unstable or other" included those living in a hostel, shelter, squat, other temporary accommodation; those staying with partner, family, or friends; and those who were homeless. "Supportive network" aimed to measure supportive relationships based on a modification of the Duke UNC Functional Social Support Questionnaire.[15] Participants scored from 1: "much less than I would like" to 5: "as much as I would like", on five items: whether they have people who care what happens to them; they receive love and affection; they get chances to talk to someone they trust; they get invited to do things; they get help when sick. Scores were classified as follows: 5–12 "least support"; 13–24 "medium support"; 25 "most support."

Ethical approval was obtained via the North West London REC 2 research ethics committee (ref 10/H0720/70).

Cross-sectional analysis

We assessed the associations of socioeconomic and social circumstance factors with ART non-adherence and virological non-suppression at the time of the questionnaire. For the non-adherence analysis, inclusion criteria were: on ART at the time of the questionnaire, a non-missing value for age, and a non-missing value for at least one of two ART-adherence questions. ART non-adherence was defined as either an affirmative response to the question: "In the past 3 months, have you ever missed your HIV treatment for 2 or more days at a time?" or reporting one or more missed doses in response to the question: "In the last 2 weeks, how many doses of HIV treatment have you missed?"

For the virological non-suppression analysis, in addition to the criteria for the non-adherence analysis, individuals were required to: have a non-missing value for clinic-recorded viral load (the latest value at the time of questionnaire, using either the study recorded value or available linked clinic data); have a non-missing value for date of ART initiation; have started ART at least 6 months before the viral load measurement being used for analysis. Virological non-suppression was defined as viral load more than 50 copies per mL.

	Cross-sectional analysis*; participants included in non-adherence analysis (N=2704)†	Longitudinal analysis‡; participants included in viral load rebound analysis (N=1740)†
Gender/sexual orientation		
Men who have sex with men	1867 (69%)	1267 (73%)
Heterosexual men	321 (12%)	171 (10%)
Women	516 (19%)	302 (17%)
Risk group		
Sex between men	1748 (65%)	1195 (69%)
Heterosexual sex	536 (20%)	314 (18%)
Injecting drug use	46 (2%)	25 (1%)
Other	353 (13%)	197 (11%)
Missing	21 (1%)	9 (1%)
Ethnic origin		
White	1875 (69%)	1259 (72%)
Black African	507 (19%)	281 (16%)
Black other	89 (3%)	52 (3%)
Other	184 (7%)	113 (6%)
Missing	49 (2%)	35 (2%)
Age		
Median (IQR)	46 (40-52)	46 (41-52)
Afford basic needs (financial hardship)§		
Always	1170 (43%)	814 (47%)
Mostly	701 (26%)	454 (26%)
Sometimes	464 (17%)	265 (15%)
No	326 (12%)	176 (10%)
Missing	43 (2%)	31 (2%)
Employment		
Employed	1479 (55%)	985 (57%)
Unemployed	483 (18%)	286 (16%)
Sick or disabled	375 (14%)	224 (13%)
Retired	180 (7%)	129 (7%)
Other	127 (5%)	79 (5%)
Missing	49 (2%)	37 (2%)
Housing		
Homeowner	914 (35%)	658 (38%)
Renting from council	840 (31%)	522 (30%)
Renting privately	609 (23%)	393 (23%)
Temporary accommodation or homeless	70 (3%)	35 (2%)
Staying with family	191 (7%)	97 (6%)
Other	10 (<1%)	6 (<1%)
Missing	40 (1%)	29 (2%)
Education (highest level)		
University degree or higher	1094 (40%)	759 (44%)
A-level or equivalent	536 (20%)	338 (19%)
O-levels or equivalent	601 (22%)	364 (21%)
Other	108 (4%)	70 (4%)
None	302 (11%)	169 (10%)
Missing	63 (2%)	40 (2%)

(Table 1 continues on the next page)

	Cross-sectional analysis*; participants included in non-adherence analysis (N=2704)†	Longitudinal analysis‡; participants included in viral load rebound analysis (N=1740)†
(Continued from previous page)		
Time in UK		
Born in UK	1513 (56%)	981 (56%)
>5 years	991 (37%)	635 (36%)
≤5 years	116 (4%)	68 (4%)
Missing	86 (3%)	54 (3%)
English reading ability		
Born in UK	1513 (56%)	981 (56%)
Fluent	912 (34%)	595 (34%)
Not fluent	208 (8%)	114 (7%)
Missing	71 (3%)	48 (3%)
Supportive network		
Most support	878 (32%)	562 (32%)
Medium support	1414 (52%)	930 (53%)
Least support	377 (14%)	227 (13%)
Missing	35 (1%)	21 (1%)
Children		
Yes	733 (27%)	426 (24%)
No	1954 (72%)	1305 (75%)
Missing	17 (1%)	9 (1%)
Partner		
Yes	1530 (57%)	997 (57%)
No	1158 (43%)	731 (42%)
Missing	16 (1%)	12 (1%)
Time since HIV diagnosis		
<2 years	180 (7%)	64 (4%)
2–5 years	361 (13%)	222 (13%)
5–15 years	1345 (50%)	926 (53%)
>15 years	755 (28%)	528 (30%)
Missing	63 (2%)	0
Number of times taking ART per day		
1	2159 (80%)	1419 (81%)
≥2	533 (19%)	309 (18%)
Missing	12 (1%)	21 (1%)
≥2 consecutive missed days of ART in the past 3 months		
No or unknown	2236 (83%)	1463 (84%)
Yes	464 (17%)	277 (16%)
Missing	4 (<1%)	2 (<1%)
≥1 missed dose in the past 2 weeks		
No or unknown	2022 (75%)	1289 (74%)
Yes	676 (25%)	447 (26%)
Missing	6 (<1%)	4 (<1%)
Non-adherent to ART¶		
No or unknown	1831 (68%)	1174 (67%)
Yes	873 (32%)	566 (33%)

(Table 1 continues on the next page)

We summarised the prevalence of ART non-adherence and virological non-suppression according to demographic, socioeconomic, and social circumstance factors; groups were compared with the χ^2 test or Cochran-Armitage test for trend for ordered categorical variables. Unadjusted and adjusted prevalence ratios for associations of socioeconomic and social circumstance factors with ART non-adherence and virological non-suppression, were generated using modified Poisson regression models.[14] For multivariable models, each socioeconomic and social circumstance factor was considered in a separate model because of high co-linearity; associations were adjusted for demographic factors (gender/sexual orientation, ethnic origin, and age). We also assessed the association between ART non-adherence and virological non-suppression with modified Poisson regression, adjusted for demographic factors.

We did a subgroup analysis in white men who have sex with men to reduce confounding by demographic, ethnic, and cultural factors. We also did a sensitivity analysis in which a viral load of more than 200 copies per mL was defined as non-suppression, because low level viraemia might not be indicative of true virological failure.

Longitudinal analysis

We did a longitudinal analysis to assess the associations of socioeconomic and social circumstance factors with risk of virological rebound. We included consenting ASTRA participants from the six centres for which linked clinic data were available. Baseline was defined as the date of questionnaire. Inclusion criteria were: on ART with viral load of 50 copies per mL or lower at baseline (latest value at the time of the questionnaire); started ART at least 6 months before the baseline viral load measurement; non-missing value for age; non-missing value for at least one ART-adherence question; and at least one viral load measurement subsequent to baseline. Individuals were followed up from baseline until virological rebound (defined as the first viral load >200 copies per mL) or the last available viral load (latest Oct 9, 2015). Follow up was not censored at ART interruption.

We assessed the unadjusted and adjusted associations of socioeconomic and social circumstance factors with subsequent virological rebound with Kaplan-Meier plots and Cox proportional hazards regression models. We used separate multivariate models for every socioeconomic and social circumstance factor, adjusted for demographic factors (gender/sexual orientation, ethnic origin, and age). Additionally, we assessed the association between ART non-adherence and viral load rebound with Cox proportional hazards regression, adjusted for demographic factors.

We did a subgroup analysis restricted to white men who have sex with men in order to reduce confounding. Two sensitivity analyses were done: virological rebound was defined as two consecutive viral load measurements more than 200 copies per mL to investigate an endpoint

of sustained viral rebound; and those who were lost to follow-up (eligible for the longitudinal analysis but date of last measurement was more than 18 months before the clinic administrative censoring date) were regarded as having experienced virological rebound 6 months after the date of the last available viral load measurement, because lack of retention in care may be associated with poorer prognosis.

Complete-case analyses were done throughout because the proportion of participants with missing data did not exceed 4% for any variable used in the analysis.

We used SAS (version 9.3) for all statistical analyses.

Role of the funding source

The funder of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication. FCL, CJS, and AS also had full access to the data.

Results

Between Feb 1, 2011, and Dec 31, 2012, 5112 HIV-diagnosed men and women were invited to participate in the ASTRA study, of whom 4200 (82%) consented to take part. 3258 individuals completed the questionnaire (response rate 64% of the 5112 individuals approached). Of the 3258 people (69% men who have sex with men, 11% heterosexual men, and 20% women) who completed the questionnaire, 2771 (85%) reported being on ART at the time of the questionnaire. Of the remaining 487 (15%) people not on ART, 366 (11%) were ART-naive individuals, 65 (2%) had stopped ART, and 56 (2%) had missing ART information. Of the 2771 participants currently on ART, 58 (2%) had missing age, and nine (<1%) had not responded to either adherence question. This resulted in 2704 individuals being included (1867 men who have sex with men, 321 heterosexual men, and 516 women; table 1).

Of the 2704 participants on ART, 873 (32%, 95% CI 31–34) reported ART non-adherence. Individuals with lower socioeconomic status by any measure (ie, increased financial hardship, non-employment, rented or unstable housing status, and non-university education) were more likely to report ART non-adherence (figure 1 and table 2). In terms of social circumstance factors, the prevalence of ART non-adherence was higher in individuals who had lived in the UK for more than 5 years but were not born in the UK, those who had non-fluent English reading ability, those who reported lower supportive network, those who had children, and those who did not have a current partner (figure 1 and table 2). After adjustment for demographic factors (gender/sexual orientation, ethnic origin, and age), all measures of poor socioeconomic status remained associated with an increased prevalence of ART non-adherence (table 2). Associations of non-adherence with non-fluent English, lower supportive network, having children, and no current partner also remained after adjustment for demographic factors, while the association with time in the UK was largely accounted for by the demographic factors (table 2). In a model that included only demographic factors, non-white ethnic origin (prevalence ratio [PR] 1·33 *vs* white, 95% CI 1·14–1·54) and younger age (PR 0·89 per 10 years older, 95% CI 0·84–0·95) were independently associated with non-adherence. However, we noted no independent association with gender/sexual orientation (PR 0·92 for heterosexual men and 0·99 for women *vs* men who have sex with men).

The virological non-suppression analysis included 2405 (89%) participants who had a recorded viral load and date of first ART initiation, and started ART more than 6 months before the viral load measurement. Of these, 219 (9%, 95% CI 8–10) had virological non-suppression (viral load >50 copies per mL; 79 [36%] with >500 copies per mL, 68 [31%] >1000 copies per mL, and 32 [15%] >10 000 copies per mL). As reported for ART non-adherence, for each of the four indicators of socioeconomic status, socioeconomic disadvantage was strongly associated with virological non-suppression (figure 1 and table 2). Additionally, individuals with non-fluent English reading ability and those who had children had an increased prevalence of virological non-suppression. There were weaker associations with non-suppression for individuals who were non-UK born and lived in the UK for more than 5 years, those who had lower supportive network, and those who had no current partner (figure 1 and table 2). Although socioeconomic

	Cross-sectional analysis*; participants included in non-adherence analysis (N=2704)†	Longitudinal analysis‡; participants included in viral load rebound analysis (N=1740)†
(Continued from previous page)		
Time on ART (years)§		
Median (IQR)	6·9 (2·8–12·4)	7·7 (3·7–12·9)
CD4 count (cells per mm³)¶		
Median (IQR)	546 (393–737)	590 (442–780)
Viral load at the time of the questionnaire		
≤50 copies per mL	2347 (87%)	1740 (100%)
>50 copies per mL	341 (13%)**	0
Missing	16 (1%)	0

Data are n (%) unless stated otherwise. ART=antiretroviral therapy. *All participants who self-reported being on ART at the time of the questionnaire and had recorded age and non-adherence information. Of these, 2405 participants had a recorded viral load and date of ART initiation, and additionally started ART >6 months before the viral load measurement and were included in viral load non-suppression analysis. †Some column percentages do not add to 1 because of rounding. ‡All participants had linked clinical data, recorded age and non-adherence information, were on ART, had viral load <50 copies per mL at the time of the questionnaire, started ART >6 months before the baseline viral load measurement, and had ≥1 subsequent viral load measurement. §Defined as having money for basic needs. ¶Self-reported ≥7 consecutive missed days of ART in the past 3 months or ≥1 missed dose in the past 2 weeks. ‖Cross-sectional N=59 and longitudinal N=0 with missing time on ART, cross-sectional N=17 and longitudinal N=2 with missing CD4 count. **Among 2405 participants that had additionally started ART >6 months before completion of the questionnaire and were included in viral load non-suppression analysis, 219 (9%) had viral load >50 copies per mL.

Table 1: Participants' characteristics

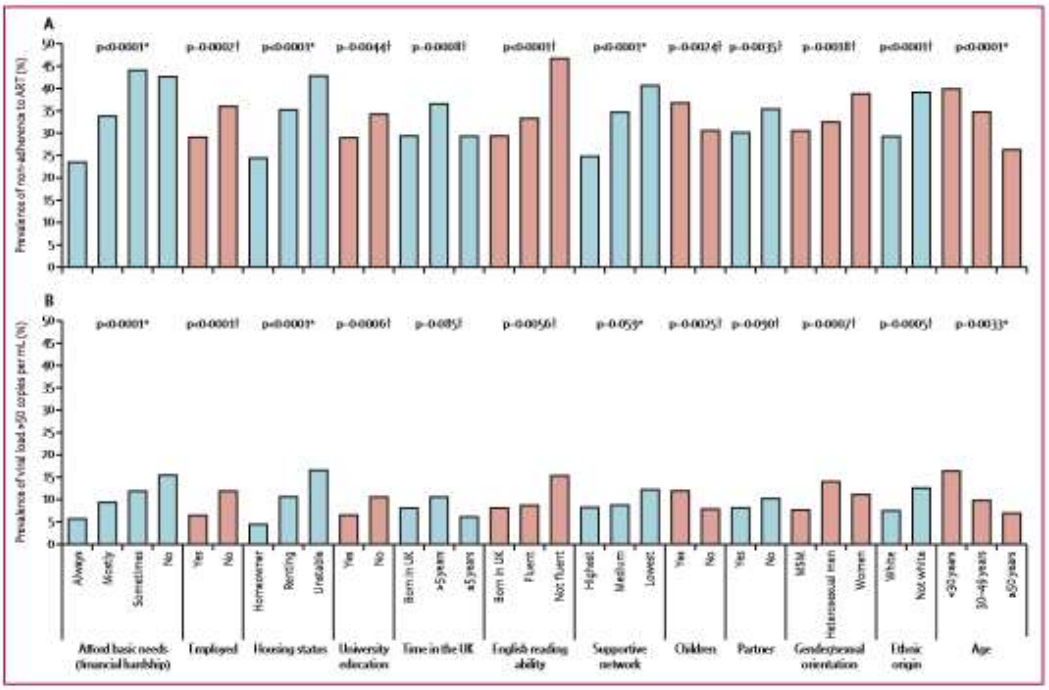

Figure 1: Prevalence of (A) antiretroviral therapy (ART) non-adherence and (B) virological non-suppression (viral load >50 copies per mL), by socioeconomic and demographic factors
(A) Data taken from a cross-sectional analysis in 2704 respondents who were on ART at the time of the questionnaire. Self-reported ≥2 consecutive missed days of ART in the past 3 months or ≥1 missed dose in the last 2 weeks. (B) Data taken from a cross-sectional analysis in 2405 respondents who were on ART and had started ART >6 months before the viral load measurement. MSM=men who have sex with men. *Calculated with Cochran-Armitage test for trend. †Calculated with χ^2 test.

disadvantage was strongly associated with non-suppression, the proportion of individuals with a viral load of more than 50 copies per mL was no more than 17% across all subgroups considered.

Table 2 also shows the adjusted associations of socioeconomic factors with virological non-suppression. The markers of lower socioeconomic status (financial hardship, non-employment, non-homeownership, and non-university education) all remained strongly associated with virological non-suppression after adjustment for demographic factors. We noted a marked trend between increasing prevalence of virological non-suppression and both increasing financial hardship and increasing housing instability. In terms of the additional social circumstance factors, having a lower supportive network and not having a current partner were associated with increased prevalence of virological non-suppression in the model adjusted for demographic factors. Living in the UK for less than 5 years was associated with lower prevalence of virological non-suppression compared with individuals born in the UK. The associations with low English fluency and having children were substantially attenuated. Because 76% of women had children compared with 7% of men who have sex with men, in unadjusted analyses the association between having children and higher prevalence of virological non-suppression could reflect an association with gender/sexual orientation.

In a model that included only demographic factors, younger age (PR 0·77 per 10 years older, 95% CI 0·66–0·88) was independently associated with virological non-suppression, and there was some evidence of associations of gender/sexual orientation (PR 1·45 for heterosexual man *vs* man who have sex with men, 95% CI 0·96–2·19 and 0·99 for women *vs* men who have sex with men, 95% CI 0·66–1·47) and ethnic origin (1·41 non-white *vs* white, 0·98–2·01) with non-suppression. Self-reported ART non-adherence was associated with 2·4 times higher prevalence of virological non-suppression (PR 2·37, 95% CI 1·84–3·07; p<0·0001), adjusted for demographic factors only.

Of 2405 participants included in the cross-sectional viral load analysis, 1740 (72%) had linked clinical data

	ART non-adherence†				Viral load non-suppression§			
	Unadjusted		Adjusted for demographic factors¶		Unadjusted		Adjusted for demographic factors¶	
	PR (95% CI)	p value‖	aPR (95% CI)	p value‖	PR (95% CI)	p value‖	aPR (95% CI)	p value‖
Enough money for basic needs? (financial hardship)								
Always	1	<0·0001**	1	<0·0001**	1	<0·0001**	1	<0·0001
Mostly	1·44 (1·24–1·66)		1·42 (1·22–1·64)		1·63 (1·15–2·30)		1·56 (1·11–2·21)	
Sometimes	1·88 (1·62–2·17)		1·81 (1·56–2·11)		2·06 (1·44–2·95)		1·84 (1·26–2·68)	
No	1·82 (1·55–2·14)		1·74 (1·46–2·06)		2·68 (1·87–3·86)		2·35 (1·60–3·43)	
Employed								
Yes	1	0·0002	1	<0·0001	1	<0·0001	1	<0·0001
No	1·24 (1·11–1·38)		1·29 (1·15–1·45)		1·85 (1·42–2·41)		1·96 (1·49–2·58)	
Housing status								
Homeowner	1	<0·0001**	1	<0001**	1	<0·0001**	1	<0·0001
Renting	1·44 (1·27–1·65)		1·34 (1·17–1·54)		2·39 (1·69–3·39)		2·09 (1·46–2·98)	
Unstable	1·76 (1·47–2·10)		1·58 (1·31–1·91)		3·70 (2·42–5·67)		2·96 (1·90–4·59)	
University education								
Yes	1	0·0041	1	0·0028	1	0·0004	1	0·0003
No	1·18 (1·05–1·33)		1·19 (1·06–1·34)		1·63 (1·23–2·16)		1·63 (1·23–2·16)	
Time in the UK								
Born in the UK	1	0·0010	1	0·086	1	0·083	1	0·044
>5 years	1·24 (1·11–1·39)		1·07 (0·93–1·24)		1·30 (1·00–1·69)		0·89 (0·65–1·22)	
≤5 years	1·00 (0·75–1·34)		0·80 (0·59–1·08)		0·75 (0·34–1·67)		0·45 (0·20–1·02)	
English reading ability								
Born in UK	1	<0·0001	1	0·0048	1	0·036	1	0·066
Fluent	1·13 (1·00–1·28)		1·00 (0·87–1·16)		1·09 (0·82–1·45)		0·77 (0·55–1·07)	
Not fluent	1·59 (1·35–1·88)		1·37 (1·12–1·67)		1·89 (1·29–2·78)		1·19 (0·74–1·93)	
Supportive network								
Most	1	<0·0001**	1	<0·0001**	1	0·071**	1	0·031
Medium	1·39 (1·22–1·60)		1·40 (1·22–1·60)		1·07 (0·80–1·44)		1·12 (0·83–1·51)	
Least	1·63 (1·38–1·93)		1·65 (1·39–1·95)		1·49 (1·03–2·15)		1·59 (1·10–2·30)	
Children								
Yes	1	0·0030	1	0·022	1	0·0053	1	0·29
No	0·83 (0·74–0·94)		0·83 (0·70–0·97)		0·67 (0·51–0·87)		0·80 (0·53–1·21)	
Partner								
Yes	1	0·0037	1	0·0014	1	0·094	1	0·026
No	1·18 (1·06–1·31)		1·20 (1·07–1·34)		1·25 (0·97–1·61)		1·35 (1·04–1·75)	

Each socioeconomic factor considered in a separate model for all results; individuals with missing values for explanatory variables were excluded. ART=antiretroviral therapy. PR=prevalence ratio. aPR=adjusted prevalence ratio. *Self-reported ≥2 consecutive missed days of ART in the past 3 months or ≥1 missed dose in the last 2 weeks. †Viral load >50 copies per mL at the time of the questionnaire. ‡Cross-sectional analysis in 2,704 respondents who were on ART at the time of the questionnaire. §Cross-sectional analysis among 2,405 respondents who were on ART and had started ART >6 months before the viral load measurement. ¶Gender/sexual orientation-ethnic origin-and age. ‖Calculated with χ^2 test. **Test for trend.

Table 2: Associations of socioeconomic factors with antiretroviral non-adherence* and virological non-suppression†

available and met the inclusion criteria for the longitudinal analysis (table 1). These individuals were followed up for 3818 person-years with a median of 2·4 years (IQR 2·0–2·7) of follow-up and a median of six (IQR 5–8) viral load measurements per person. During this period, eight (<1%) individuals died. During follow-up, 139 (8%) people had virological rebound, corresponding to a rate of 3·6 per 100 person-years (95% CI 3·0–4·2). By 12 and 24 months of follow-up, the Kaplan-Meier estimates of virological rebound were 3·9% (95% CI 3·0–4·8) and 7·0% (5·7–8·2), respectively.

In unadjusted Cox regression analysis, increased financial hardship, non-employment, and rented or unstable housing status were strongly predictive of increased risk of virological rebound (figure 2 and table 3). We noted a more modest association between non-university education and increased rebound risk (figure 2D and table 3). Additionally, having children and not having a partner were associated with a higher risk of rebound; data also suggested an association with lower supportive network. The pattern of associations remained, with some attenuation for some factors, after

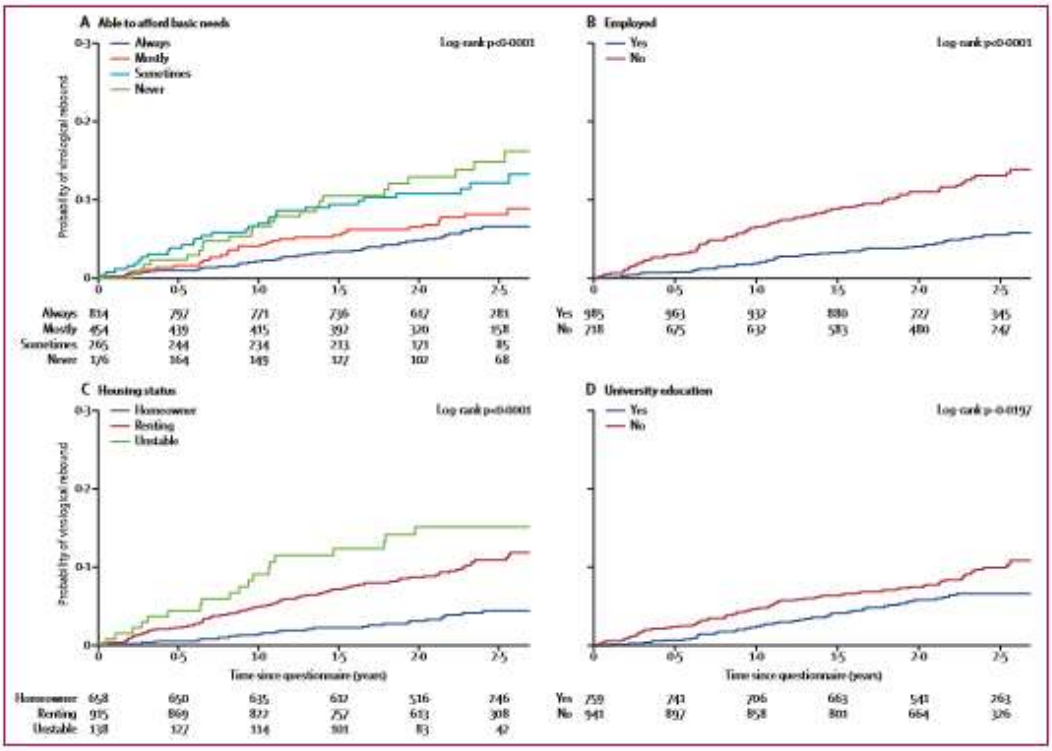

Figure 2: Kaplan-Meier plots of time until virological rebound (viral load >200 copies per mL) according to (A) ability to afford basic needs (financial hardship), (B) employment status, (C) housing status, and (D) university education

Longitudinal analysis in 1,140 respondents on ART with viral load <50 copies per mL at the time of the questionnaire. Individuals with missing values were excluded. Numbers provided indicate the number of individuals at risk.

See Online for appendix

adjustment for demographic factors (table 3). In a model for viral load rebound containing only the demographic factors, there were independent associations of gender/sexual orientation (HR 2·00 for heterosexual men *vs* men who have sex with men, 95% CI 1·15–3·47; HR 1·45 for women *vs* men who have sex with men, 95% CI 0·87–2·41) and younger age (PR 0·74 per 10 years older, 95% CI 0·61–0·90) with virological rebound, but no evidence of association with ethnic origin (HR 1·32, 95% CI 0·83–2·09 for non-white *vs* white). Individuals who self-reported ART non-adherence at baseline had more than three times the rate of virological rebound compared with individuals who did not (HR 3·11, 95% CI 2·20–4·38; p<0·0001, adjusted for demographic factors only).

Among the subgroup of white men who have sex with men, the markers of lower socioeconomic status remained strongly associated with increased prevalence of ART non-adherence and virological non-suppression, and increased rates of virological rebound (appendix pp 1, 2). Results of all sensitivity analyses for cross-sectional and longitudinal analyses were broadly consistent with those of the main analyses (appendix pp 3, 4).

Discussion

This is the first study to assess the effect of socioeconomic status on virological outcomes in people receiving treatment for HIV in the UK. In this setting of universal access to health care and high levels of treatment success, all four markers of lower socioeconomic status considered (financial hardship, non-employment, rented or unstable housing status, and non-university education) were strongly associated with ART non-adherence and virological non-suppression on ART. Furthermore, each of the four markers of lower socioeconomic status was predictive of subsequent virological rebound in people

with viral suppression at baseline. These results provide evidence of the importance of current socioeconomic disadvantage in determining virological outcomes of ART. The adverse implications of poorer socioeconomic status clearly go beyond inability to pay for treatment and health care, and operate strongly even in people engaged with clinical care.

In previous European studies[9,10] of socioeconomic status and ART outcomes in which education level was used as the sole indicator of socioeconomic status, lower education level was associated with virological non-suppression in two of three studies. Two additional European studies considered employment status and noted that unemployment was associated with twice the adjusted risk of virological failure[11] and that viral load of more than 50 copies per mL was associated with twice the unadjusted odds of developing inability to work among those able to work when starting ART.[12] In terms of mortality risk, in a French study of individuals starting ART, social vulnerability (combining education, employment, and housing status) was associated with 20% increased mortality risk after adjustment for behavioural and biomedical factors.[13] The results of this present analysis add to existing findings showing strong associations between current markers of poverty and hardship and viral load response to ART in people with HIV in the UK.

Adherence to treatment is the strongest determinant of virological response to ART.[14] The strong association between socioeconomic factors and ART non-adherence, and between non-adherence and virological outcomes, suggest that associations between low socioeconomic status and virological non-suppression are probably mediated mainly through ART non-adherence. It is important to appreciate the apparent substantial effect of socioeconomic factors on non-adherence, even in the current era of simpler and more tolerable drugs, with most participants on once a day regimens. There are a number of reasons why people with greater levels of social or financial disadvantage might have greater difficulties maintaining treatment adherence, including competing responsibilities and stress, unsettled living circumstances, food insecurity (particularly when ART regimen requires food),[27] increased prevalence of mental health problems,[28] stigma and low self-esteem, or less knowledge about the importance of adherence.[29] It is also conceivable that part of the effect of socioeconomic status on virological outcomes is independent of non-adherence, for example related to factors such as late diagnosis,[30] low CD4 count or AIDS at ART initiation,[31] differences in experiences or quality of health care, and pharmacokinetics through absence of sufficient food.[32]

The results of this study have practical implications to guide the identification of individuals on ART who are at higher risk of ART non-adherence and poorer treatment outcomes. Individuals with difficult socioeconomic circumstances might benefit from specific support with ART adherence such as prescription of less complex regimens,[33] or interventions such as peer support.[34] Moreover, the results show that the success of treatment cannot be separated from the social context in which it occurs. They emphasise the importance of a holistic approach to HIV care, with awareness that difficulties in individuals' circumstances affect treatment success, and good links to social care services that can support individuals in addressing difficulties with finance and benefits, housing, and employment issues. However, our findings also raise the agenda of socioeconomic inequalities in health in a wider context, adding to existing evidence of the adverse effect of poverty and social

	N	Rate per 100 person-years	Unadjusted		Adjusted for demographic factors†	
			HR (95% CI)	p value‡	aHR (95% CI)	p value§
Enough money for basic needs? (financial hardship)						
Always	814	2·49	1	<0·0001§	1	0·0005§
Mostly	454	3·64	1·47 (0·95–2·27)		1·34 (0·86–2·09)	
Sometimes	265	5·60	2·25 (1·43–3·55)		1·86 (1·15–3·01)	
No	176	6·95	2·78 (1·71–4·53)		2·34 (1·39–3·92)	
Employed						
Yes	985	2·26	1	<0·0001	1	<0·0001
No	718	5·78	2·56 (1·81–3·62)		2·95 (2·05–4·25)	
Housing status						
Homeowner	658	1·70	1	<0·0001§	1	<0·0001§
Renting	915	4·76	2·80 (1·81–4·32)		2·40 (1·52–3·79)	
Unstable/other	138	6·95	4·11 (2·27–7·42)		3·30 (1·77–6·13)	
University education						
Yes	759	2·79	1	0·021	1	0·014
No	941	4·24	1·52 (1·07–2·17)		1·57 (1·10–2·26)	
Time in the UK						
Born in UK	983	3·09	1	0·11	1	0·51
In UK >5 years	635	4·47	1·44 (1·02–2·04)		0·95 (0·61–1·48)	
In UK <5 years	68	2·96	0·95 (0·35–2·59)		0·54 (0·19–1·54)	
English reading ability						
Born in UK	983	3·09	1	0·14	1	0·81
Fluent	595	4·35	1·40 (0·98–2·00)		0·92 (0·59–1·42)	
Not fluent	114	4·43	1·43 (0·74–2·78)		0·78 (0·37–1·66)	
Supportive network						
Most support	562	3·07	1	0·070§	1	0·044§
Medium support	930	3·68	1·20 (0·81–1·77)		1·20 (0·81–1·87)	
Least support	227	5·04	1·63 (0·98–2·72)		1·76 (1·05–2·94)	
Children						
Yes	426	6·03	1	<0·0001	1	0·014
No	1305	2·91	0·49 (0·34–0·68)		0·53 (0·32–0·88)	
Partner						
Yes	997	2·96	1	0·0081	1	0·0021
No	731	4·65	1·57 (1·12–2·19)		1·71 (1·21–2·40)	

Every socioeconomic factor was considered in a separate model for all results; individuals with missing values for explanatory variables were excluded. HR=hazard ratio. aHR=adjusted hazard ratio. *Longitudinal analysis in 1,740 respondents on ART with viral load <50 copies per mL at the time of the questionnaire. †Gender/sexual orientation, ethnic origin, and age. ‡Calculated with χ² test. §Test for trend.

Table 3: Associations of socioeconomic factors with virological rebound (viral load >200 copies per mL)*

disadvantage on health outcomes.[34] Socioeconomic factors are often not incorporated in clinical research studies of HIV; however, our results show that such factors are likely to be profound determinants of HIV outcomes. As such, there is a need for systematic collection of socioeconomic factors in HIV clinical care and research.

There are some limitations to this study. The ASTRA questionnaire study response rate was 64%: non-responders might differ from responders with regard to socioeconomic factors and association with virological outcomes. Our sample had a lower proportion of black African individuals, a lower proportion of individuals who acquired HIV through heterosexual sex, and a greater proportion of men who have sex with men than among people living with HIV in the UK generally.[35] We did not account for whether participants were on first-line or subsequent ART regimens, and the specific regimen used. Our measures of socioeconomic status and adherence to ART were collected at one timepoint only and by self-report. We did not include 65 individuals who had previously been on ART but were not on ART at the time of the questionnaire; when this group were included in cross-sectional analyses as non-adherent, the prevalence of non-adherence and non-suppression was slightly higher than seen in the main analysis (34% *vs* 32%, and 11% *vs* 9% respectively), but socioeconomic associations were unchanged (data not shown). In the cross-sectional analysis, only association can be studied; it is not possible to rule out the presence of reverse causality for some factors. However, all findings are reinforced in the longitudinal analysis, which is unlikely to suffer from this bias. Longitudinal time-to-rebound analyses are potentially subject to bias if frequency of viral load monitoring differs according to explanatory variables; however, the median number of viral load measurements during follow-up was very similar across socioeconomic subgroups (data not shown).

In summary, even in a European setting with free access to HIV treatment and overall high rates of treatment success, socioeconomic disadvantage substantially affects HIV treatment outcomes. Emphasis should be placed on supporting adherence of people in these higher risk groups. Socioeconomic factors should be taken into account when designing clinical management strategies including linkage to the relevant social care agencies. Further research is needed on specific interventions that reduce socioeconomic inequalities in HIV-outcomes.

Contributors

FCL, ANP, AJR, AS, JA, LS, AMG, RG, MF, JE, SC, and MAJ were members of the team who devised the ASTRA study. AJR, AS, JA, RG, MF, RO'C, MJ, and MAJ took part in data collection. LSB, FCL, and CJS conceived the idea for the specific analysis and developed the analysis plan with approval from all authors. LSB analysed data, with additional input from FCL and CJS, and wrote the first draft of the report. JA, LS, AJR, RO'C, AMG, RG, MF, JE, MJ, SC, YA, ANP, AS, and MJ reviewed and commented on this and subsequent drafts. All authors approved the final version of the report.

Declaration of interests

The authors declare the following conflicts of interest outside of the submitted work: CJS receives personal fees from Gilead Sciences and ViiV Healthcare. JA receives grants, personal fees, and non-financial support from Gilead Sciences; personal fees from ViiV and MSD, Janssen, and BMS. AMG receives grants and personal fees from ViiV, Gilead, BMS, and Janssen; and personal fees from Abbott, Pfizer, AbbVie, and MSD. RG receives grants from Gilead Sciences, GSK, ViiV, Pfizer, Merck, BMS, and Janssen. At the time of his death MF had received honoraria, support to attend meetings, and lecture fees or research funding from AbbVie, BMS, Gilead, Janssen, Merck, and ViiV. ANP receives personal fees from GSK Biologicals, Gilead, and AbbVie. LSB, LS, AJR, RO'C, JE, MJ, SC, YA, AS, MAJ, and FCL declare no competing interests.

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